Indium catalysed electrophilic aromatic substitution

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INDIUM CATALYSED ELECTROPHILIC AROMATIC SUBSTITUTION

Submitted by Joseph P. Hartley

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INDIUM CATALYSED ELECTROPHILIC AROMATIC SUBSTITUTION

CONTENTS

ABBREVIATIONS

Ac	acyl
acac	acetoacetate
Aq.	aqueous
Ar	aryl
Bn	benzyl
BTF	trifluorotoluene
Bu	butyl
$CDCl_3$	deuterated chloroform
CTf_3	tris(trifluoromethanesulfonyl)methide
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
Et	ethyl
EtOAc	ethyl acetate
ee	enatiomeric excess
equiv.	Equivalent
FAB	Fast Atom Bombardment
h	hour
HQD	hydroxyquinuclidine
Hz	Hertz
J	coupling constant
LA	Lewis acid
m	meta
m	multiplet

Me	methyl
MeCN	acetonitrile
MeOH	methanol
mol.	molecular
NMR	nuclear magnetic resonance
NTf_2	bis(trifluoromethanesulfonyl)amide
Nuc	nucleophile
o	ortho
OMe	methoxy
OTf	trifluoromethanesulfonate
ONf	nonafluorobutanesulfonate
p	para
Ph	phenyl
Pr	propyl
ppm	parts per million
rt	room temperature
s	singlet
Sat.	saturated
SDS	sodium dodecylsulfate
t	triplet
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Tol	tolyl
Ts	tosyl
q	quartet

ACKNOWLEDGEMENTS

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I would like to thank my parents, and my brothers Chris, Nick, Pat and Benji for their help and support through the last 3 years. Thanks also for the loan of the PC, which was of invaluable help in producing this work.

Finally, my deepest gratitude goes to Amanda, for all her love, support and encouragement that has been vital over the last three years. You're a star.

Dedicated to

Mum, Dad and the boys

ABSTRACT

The catalytic efficacy of indium(III) salts, including indium triflate and the novel complex indium triflamide, has been investigated in a number of electrophilic aromatic substitution reactions. Lower catalyst loadings, a wider scope of substrates and higher yields have been achieved with respect to other Lewis acids.

The Friedel-Crafts acylation of electron rich aromatics has been achieved in high yield using a potent combination of indium and lithium salts. Indium salts have also been found to be exceptional catalysts for Friedel-Crafts benzoylation and sulfonylation reactions, furnishing the corresponding diaryl ketones and sulfones in high yield. Indium triflate is among the most efficient catalysts reported for these reactions.

Indium complexes have also been employed successfully as catalysts for aromatic nitrations, replacing the use of concentrated sulfuric acid. The only side product is water and the catalysts may be recycled and reused, presenting an environmentally acceptable procedure.

The reaction of aromatics with dialkyl sulfamoyl chlorides presents a facile route to aryl sulfonamides. Indium triflate was found to be the most efficient Lewis acid catalyst for this demanding process.

CHAPTER 1

INTRODUCTION

1 Introduction

1.1 Indium and its Applications

Until very recently the interest in indium and its applications lay in low melting-point alloys and solders, display devices and semiconductors. While boron or aluminium reagents have been the subject of considerable interest, the use of indium in organometallic reactions was limited, due, primarily, to its low natural abundance (0.1 ppm, comparable with silver) and the fact that organoindium compounds are less reactive than alkyllithiums and Grignard reagents.

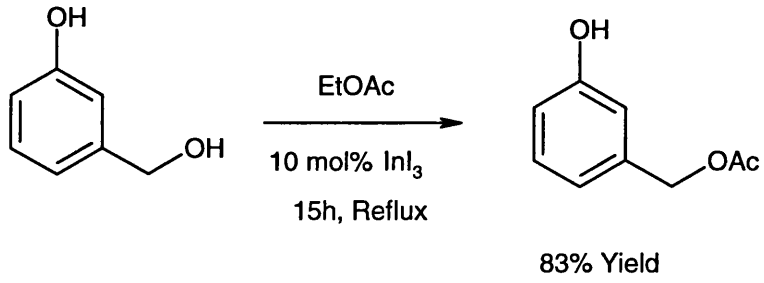
However, the discovery that indium metal can react with an organic substrate to generate an organoindium species *in situ*, means that the use of sensitive, toxic or expensive organometallics can be avoided. Thus, allylation, cyclopropanation and Reformatsky reactions can be affected using indium metal and the corresponding allyl halides, methylene dibromides and α-haloesters.[1] Whilst indium is not unique in its ability to carry out such reactions (it is comparable with tin and zinc), its exceptional stability to water and air allows such reactions to be carried out under aqueous conditions. The associated practical advantages of water as a solvent has led to an explosion of interest in indium mediated processes.[1,2]

Recently, indium(III) complexes have received a great deal of interest as Lewis acid catalysts. Although comparatively weak when compared to their aluminium and boron counterparts, indium(III) salts are stable to water and are reusable. This introduction serves to detail the use of indium(III) salts as Lewis acids in organic synthesis.

1.2 Indium(III) Lewis acids in Organic Synthesis

Transesterification of esters to the corresponding analogues with higher alcohol moieties is well documented, however the reverse transformations are not. Ranu and co-workers resolved this difficulty, utilising indium iodide with success. The reaction provides a simple and effective method for transesterification and is superior to reported aluminium and titanium reagents.[3] Transesterification to a *tert*-butyl ester, which is often problematic in acid-catalysed reactions, has been realised using this method.

In an extension of this methodology, the same group carried out indium iodide-catalysed heteroatom acylation using ethyl acetate in a transesterification process.[4] 10 mol% InI_3 (prepared *in situ* from indium metal and iodine) in an excess of refluxing ethyl acetate catalyses the acylation of amines and primary alcohols in the presence of secondary and phenolic alcohols (Scheme 1).

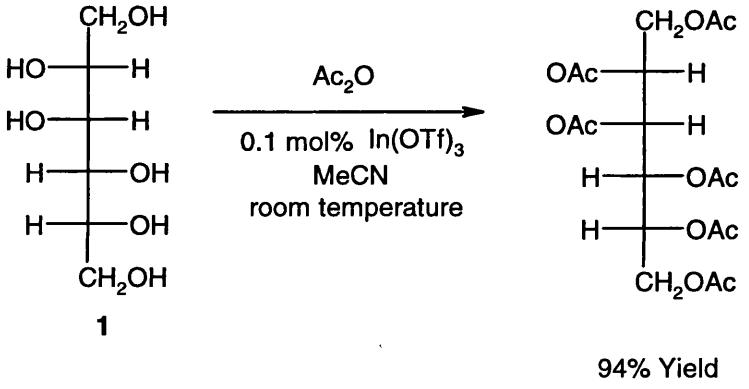


Scheme 1

The same system has been employed in the conversion of MOM- and tetrahydropyran- protected alcohols to the corresponding acetates in one step.[5,6] The

reaction was chemoselective for primary alcohols; secondary and phenolic ethers were simply deprotected to the parent alcohols.

The Frost group have reported the use of using indium triflate in the acylation of alcohols and amines with acetic anhydride under very mild conditions.[7] Acylation of heteroatoms in excellent yield at room temperature may be achieved with catalyst loadings as low as 0.1 mol%. Even polyhydroxy compounds such as D-mannitol **1** are acylated in excellent yield (Scheme 2). Sub-stoichiometric indium triflate in combination with stoichiometric lithium perchlorate promotes the acylation of alcohols with isopropenyl acetate, generating acetone as the predominant side-product.[8]

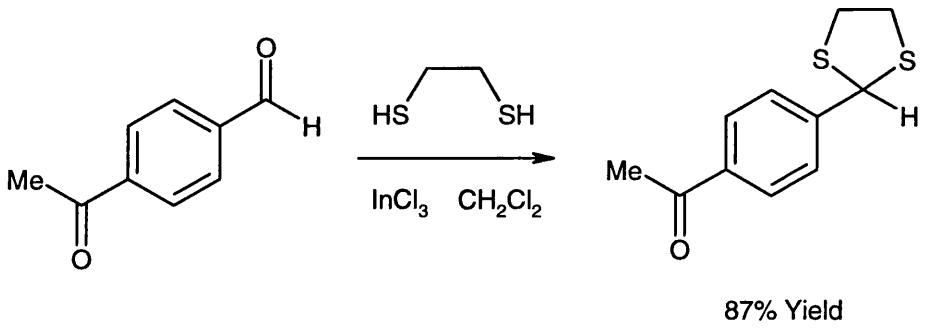


Scheme 2

The conversion of aldehydes to *gem*-diacetates in high to quantitative yields using a sub-stoichiometric amount of indium trichloride was reported by Yadav and co-workers.[9] A range of aryl and alkyl aldehydes were readily converted to the corresponding diacetates at room temperature, although ketones did not react. The subsequent deacetylation can be achieved using water and sub-stoichiometric indium trichloride.

1,3-dithianes are widely used tools for the formation of carbon-carbon bonds. The dithioacetalistion of aldehydes with thiols is usually catalysed by protic or Lewis acids. Problems associated with reported Lewis acid-catalysed processes include long reaction times, stoichiometric amounts of reagents, excess of thiols, anhydrous conditions and poor selectivity between aldehydes and ketones. Two groups have reported the use of sub-stoichiometric indium(III) halides in thioacetalisation reactions under mild conditions. A Brazilian group detailed the use of 10 mol% indium bromide in organic and aqueous media, although the scope of the reaction in water was more limited than it was in dichloromethane.[10]

Muthusamy and co-workers reported that 5 mol% indium trichloride catalyses the thioacetalisation of aldehydes in high yields.[11] Reaction times varied from 10 minutes to 28 hours. Excellent chemoselectivity is shown in the thioacetalisation of keto-aldehydes, where only the aldehyde group is reacted (Scheme 3).

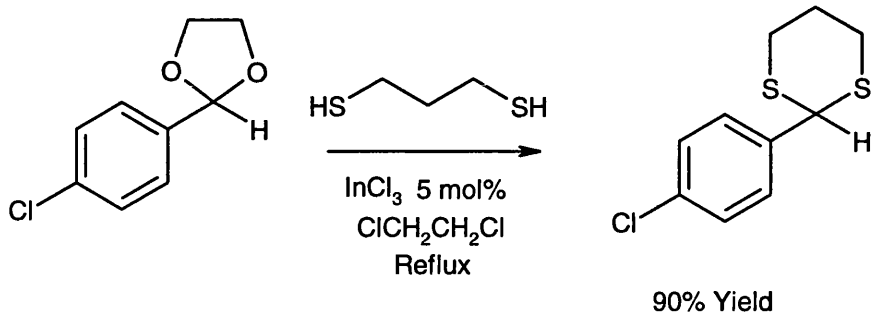


87% Yield

Scheme 3

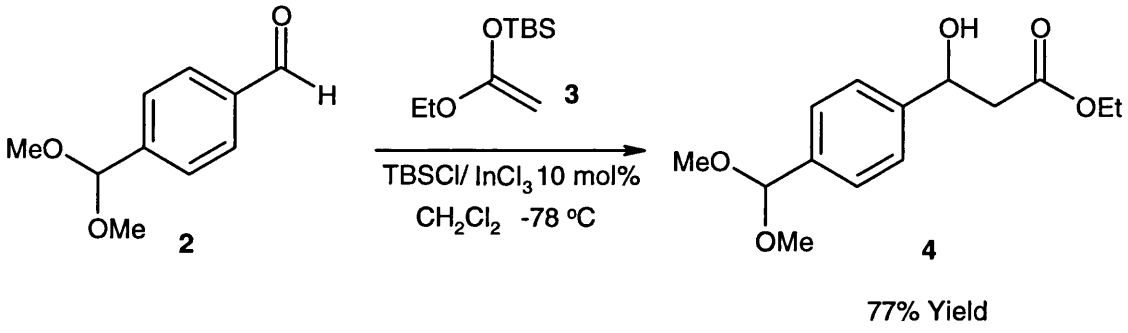
Ranu and co-workers have shown indium trichloride catalyses the transthioacetalisation of *O,O*-acetals in excellent yields under mild conditions.[12] This process bypasses the intermediate step of deprotection to the parent aldehyde. Cyclic

and acyclic *O,O*-acetals undergo clean transthioacetalisation with very short reaction times (Scheme 4).



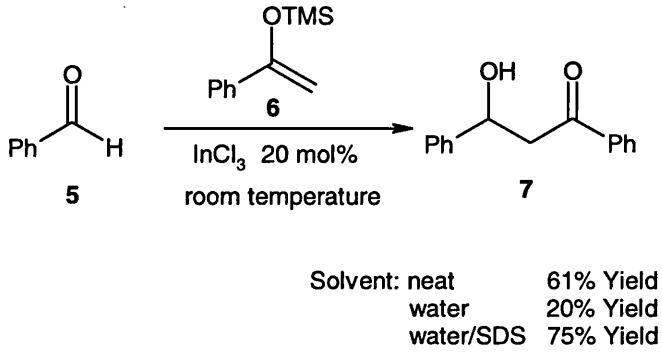
Scheme 4

Kobayashi and co-workers reported combination of indium trichloride and chlorotrimethylsilane catalyses the aldol reaction between aldehydes or dimethyl acetals with trimethylsilyl enol ethers.[13] By using an alternative silyl enol ether, one could achieve preferential activation of aldehydes in the presence of the corresponding acetals. Thus, aldehyde **2** reacts with *tert*-butyldimethylsilyl enol ether **3** to give the aldol product **4** as the sole product (Scheme 5).



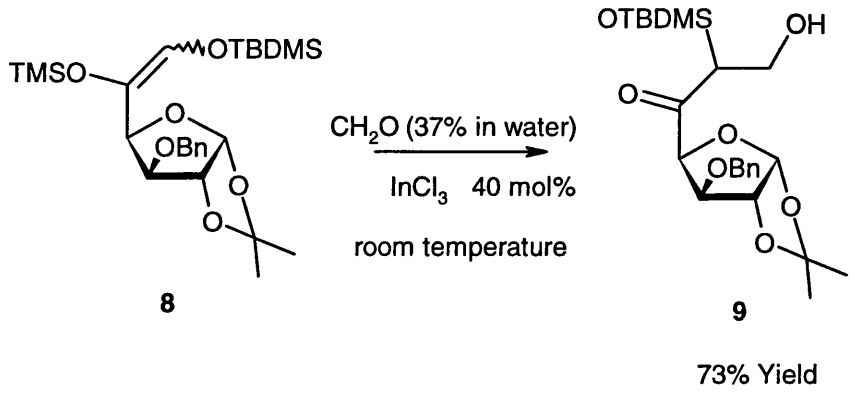
Scheme 5

Indium trichloride is an efficient catalyst in Mukaiyama aldol reactions of aldehydes with silyl enol ethers in water at room temperature.[14] In an improved methodology, Kobayashi and co-workers showed that the addition of small amounts of surfactant to water leads to a more efficient reaction media.[15] This is shown in the reaction of benzaldehyde **5** with silyl enol ether **6** to give aldol product **7** (Scheme 6).



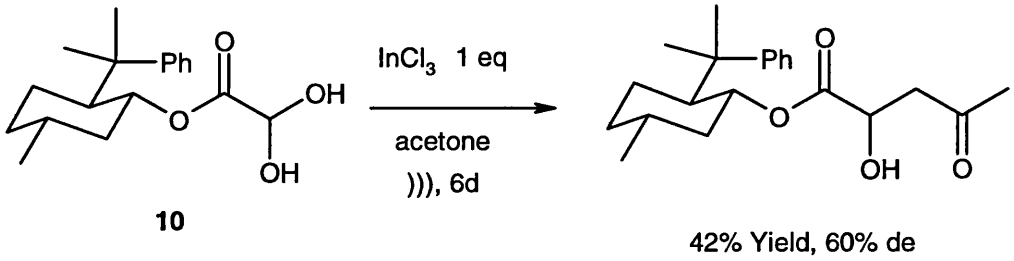
Scheme 6

Loh and co-workers have applied this methodology to the chain elongation of the glucose-derived silyl enol ether **8** with commercially available aqueous formaldehyde solution to give **9** (Scheme 7).[16]



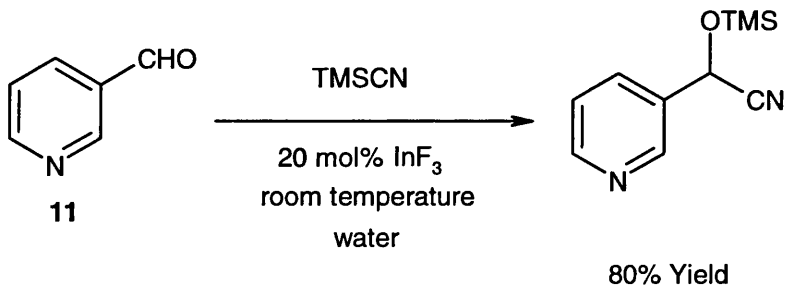
Scheme 7

Aldol reactions involving glyoxylate or glyoxylic acid have, in most cases, proved inefficient despite harsh reaction conditions.[17] Loh and co-workers reported that indium trichloride promotes the reaction of ketones with glyoxylic acid and methyl glyoxylate under sonication, furnishing the biologically and synthetically important α-hydroxy acids and esters in excellent yields.[18] By employing a chiral glyoxylate **10,** α-hydroxy esters were obtained with good diastereoselctivities (Scheme 8).



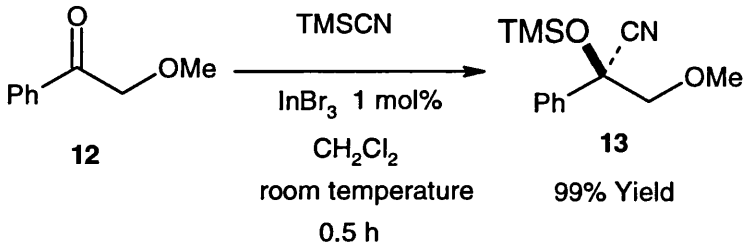
Scheme 8

Indium trifluoride (30 mol%) catalysed the addition of TMSCN to aldehyde **11** in aqueous media at room temperature (Scheme 9).[19] The products of these reactions are versatile synthetic intermediates, allowing access to α-hydroxy aldehydes, α-hydroxy ketones, α-amino acids and β-hydroxy amines. Loh and co-workers showed that the addition is chemoselective for aldehydes over ketones, and that sub-stoichiometric indium trifluoride is superior even to stoichiometric $InCl_3$.



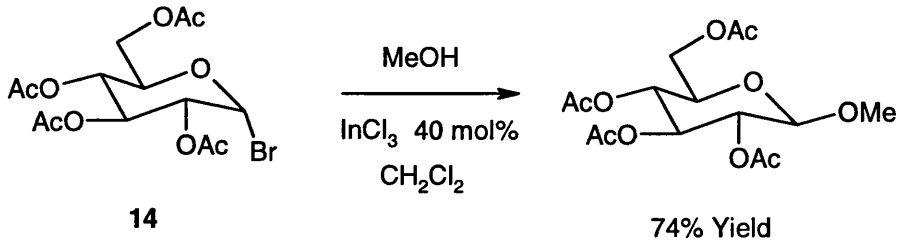
Scheme 9

An Italian group have shown that indium(III) salts are effective catalysts for the cyanation of ketones, a more demanding process than the cyanation of aldehydes or imines.[20] On screening a range of Lewis acids, indium tribromide was found to be the most effective catalyst for the addition of TMSCN to α-methoxy acetophenone **12** to give trimethylsilyloxy cyanohydrin **13** (Scheme 10). Under mild conditions (1 mol% catalyst, room temperature) a range of α-hetero-substituted and unsubstituted ketones underwent cyanation to give the corresponding cyanohydrin in moderate to excellent yield.



Scheme 10

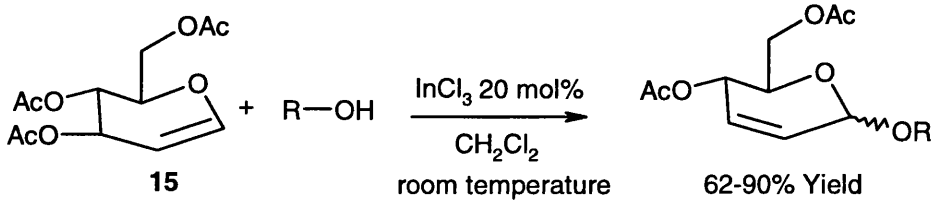
The formation of oligosaccharides through the glycosidation reaction of glycosyl bromides is usually catalysed by toxic heavy metals such as $HgO/HgBr_2$ or $Ag_2CO_3/AgClO_4$. Chowdary and co-workers have detailed the efficient use of sub-stoichiometric indium trichloride in coupling glycosyl bromides with alcohols.[21] In all cases glycosides and disaccharides were obtained with pronounced β selectivity in good to high yield, for example glycosyl bromide **14** coupled with methanol in the presence of 40 mol% indium trichloride (Scheme 11).



14 74% Yield

Scheme 11

Indium trichloride has been shown as an efficient catalyst for the synthesis of alkyl and aryl 2,3-unsaturated glycopyranosides via the Ferrier rearrangement.[22] In the presence of sub-stoichiometric $InCl_3$ (20 mol%), tri-*O*-acetyl-D-glucal **15** reacts with a range of alcohols in high yield (Scheme 12). Where a monosaccharide is used, the disaccharide is formed in good yield. $InCl_3$ has been shown to have superior catalytic activity than a number of Lewis acids including BF_3, $SnCl_4$, $LiBF_4$ and $LiClO_4$.

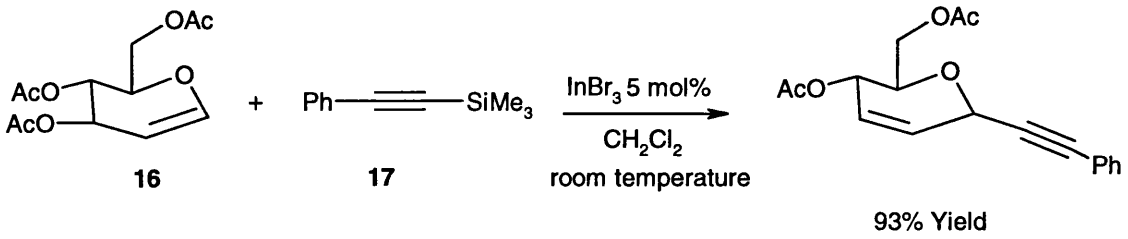


15 62-90% Yield

Scheme 12

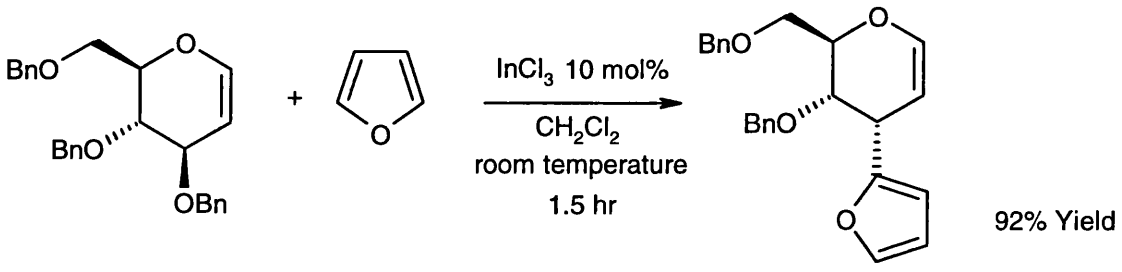
Yadav and Reddy have shown that glucals react smoothly with silyl nucleophiles in the presence of sub-stoichiometric indium tribromide to form *C*-glycosides,[23] versatile chiral building blocks for the synthesis of many bioactive compounds. Allyl trimethylsilane, trimethylsilylcyanide and trimethylsilylazide reacted with various glycals to give the corresponding C-pseudoglycals in excellent yields. The α-anomer was obtained as the major product in each case and the catalyst was easily recovered from the aqueous layer on work-up.

This methodology has also been applied to the reaction of glycals with alkynylsilanes to afford the corresponding alkynyl sugars in excellent yields.[24] Thus, treatment of 3,4,6-tri-*O*-acetyl-D-glucal **16** with phenyl (trimethylsilyl)acetylene **17** in the presence of 5 mol% indium bromide at ambient temperature results in the formation of the corresponding alkynyl *C*-glycoside in 93% yield (Scheme 13). The α-anomer was obtained as the predominant product.



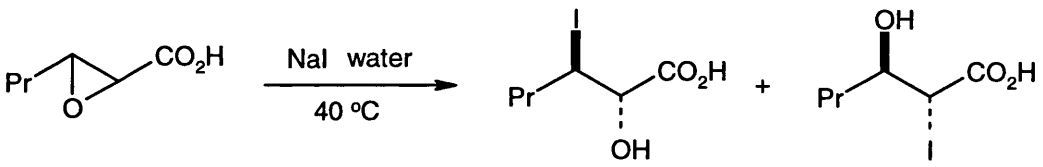
Scheme 13

The same group have also shown that glycals react with heterocycles in the presence of a sub-stoichiometric amount of indium trichloride to provide C_3 substituted glycals.[25] Such substrates constitute intermediates in the synthesis of a range of *C*-glycosides bearing carbon-linked heterocycles, potent bioactive molecules. Whilst furan and pyrrole reacted at the C_3 position of the glucal, 2-benyloxymethylfuran, thiophene and *N*-Boc indole reacted at the C_1 position (Scheme 14).



Scheme 14

The ring opening of α-β-epoxy carboxylic acids by halide ions yields carboxyhalohydrins, important synthetic intermediates, precursors of such compounds as α-hydroxy-β-amino- and α-amino-β-hydroxycarboxylic acids. Pizzo and co-workers reported the indium halide catalysed bromolysis and iodolysis[26] of α-β-epoxy carboxylic acids in water with a high degree of regio- and stereoselectivities. Bromolysis of α-β-epoxy carboxylic acids with NaBr at pH 2.0 proceeds with excellent β selectivity in the presence of 10 mol% indium tribromide. Iodolysis with NaI at pH 1.5 is catalysed by 10 mol% indium trichloride and gives the β-iodo -α-hydroxy carboxylic acids with excellent selectivity (Scheme 15). At pH 4.0, in the absence of Lewis acid the selectivity is reversed, giving the α-iodo -β-hydroxy carboxylic acids. At no time is the α,β-diol observed.

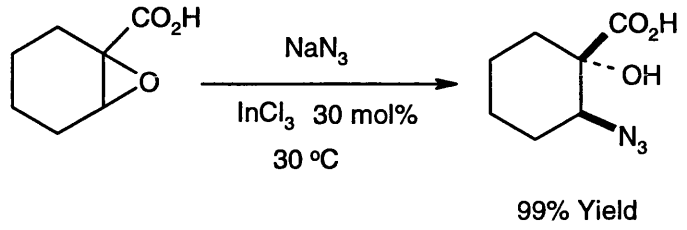


$InCl_3$	0.5 h, pH 1.5	98	:	2
	64 h, pH 4.0	1	:	99

Scheme 15

The same group have shown indium trichloride to be an efficient catalyst for the azidolysis of α-β-epoxy carboxylic acids with sodium azide.[27] In an aqueous solution at pH 4.0, $InCl_3$ catalyses the formation of β-azido-α-hydroxy carboxylic acids in excellent yields and high diastero- and regioselectivity (>99%). The reaction is sluggish when run in the absence of catalyst, in organic solvents or at neutral pH. A

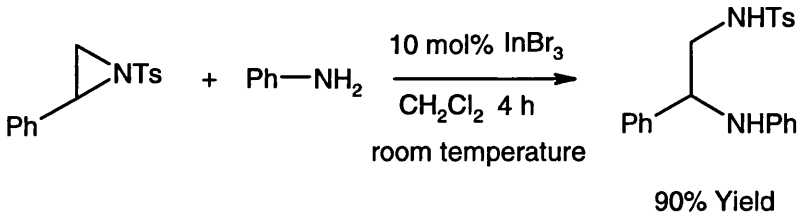
range of mono- and disubstituted α-β-epoxy carboxylic acids undergo azidolysis under these conditions (Scheme 16).



Scheme 16

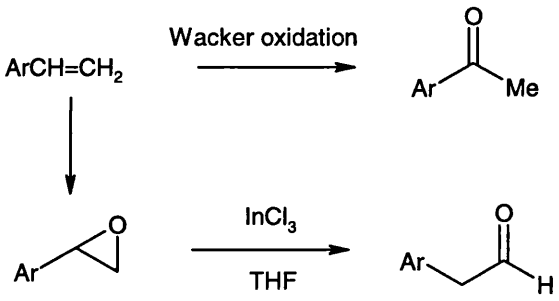
Yadav and co-workers reported the indium triflate catalysed ring opening of aziridines with carboxylic acids to give β-aminoesters in high yield.[28] The reactions proceed smoothly at room temperature in the presence of 5 mol% catalyst. Aryl-*N*-tosyl aziridines underwent attack at the benzylic position, whilst alkyl-*N*-tosyl aziridines underwent terminal cleavage. Likewise, *N*-Tosylaziridines are opened regioselctively with trimethylsilyl azide in the presence of indium trichloride to afford the corresponding azido amines in high yield.[29]

The same group has also detailed the indium tribromide catalysed aminolysis of activated aziridines with anilines under mild conditions.[30] Vicinal amines are formed in high yield (78-92%) at ambient temperature. Styrene-*N*-tosyl aziridine underwent cleavage in a regioselective manner with attack occurring at the benzylic position (Scheme 17). Indium tribromide was found to be a superior catalyst to $InCl_3$, $CeCl_3$, YCl_3 and $YbCl_3$.



Scheme 17

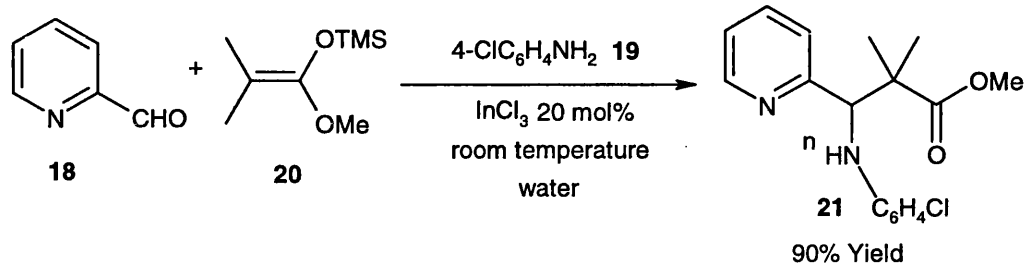
The Ranu group have reported a simple and efficient procedure for the rearrangement of substituted epoxides catalysed by indium trichloride.[31] Aryl substituted epoxides isomerise with complete regioselectivity to form a single carbonyl compound. This procedure, in combination with an epoxidation reaction offers a viable alternative to the Wacker oxidation of vinyl arenes (Scheme 18)



Scheme 18

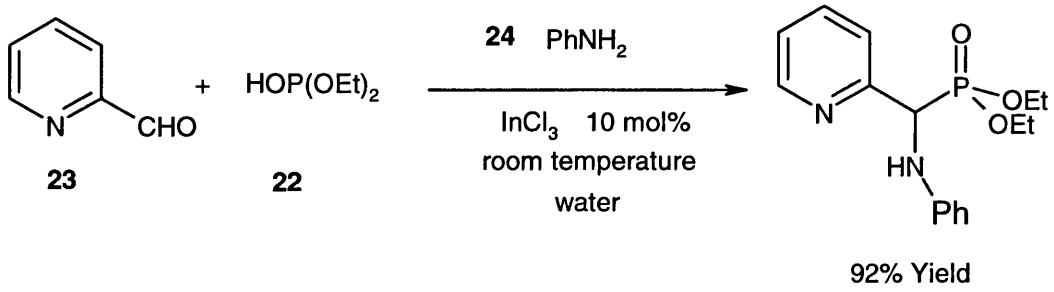
The Mannich reaction is a classic method for preparing β-amino acids, esters, ketones and aldehydes. To circumvent the problems associated with synthesis and purification of imines, an elegant one-pot Mannich-type reaction has been developed employing indium trichloride as catalyst.[32] The reaction between aldehyde **18**, amine **19** and silyl enol ether **20** is catalysed by 20 mol % indium trichloride in water and affords the β-

aminoester **21** in high yield (Scheme 19). The use of glyoxylic acid monohydrate yields α-amino acids, although yields ranged from low to moderate.[33]



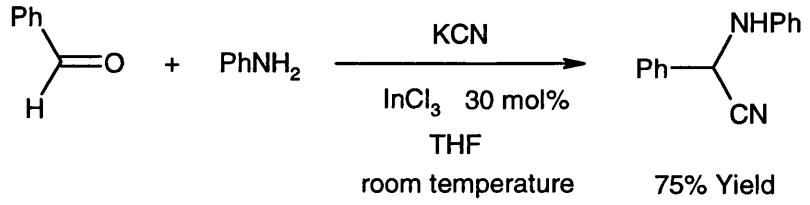
Scheme 19

A similar strategy has been used by Ranu and co-workers in a one-pot synthesis of α-amino phosphonates from the 3-component condensation of carbonyl compounds, amines and diethylphosphite **22**.[34] Whilst indium trichloride catalyses the reaction of aldehydes smoothly at room temperature, high temperatures are required for the reaction of ketones. The reaction is tolerable of functional groups as shown in the reaction of pyridine-derived aldehyde **23** with aniline **24** and **22** (Scheme 20). The products of these reactions are particularly useful as amino-acid mimics.



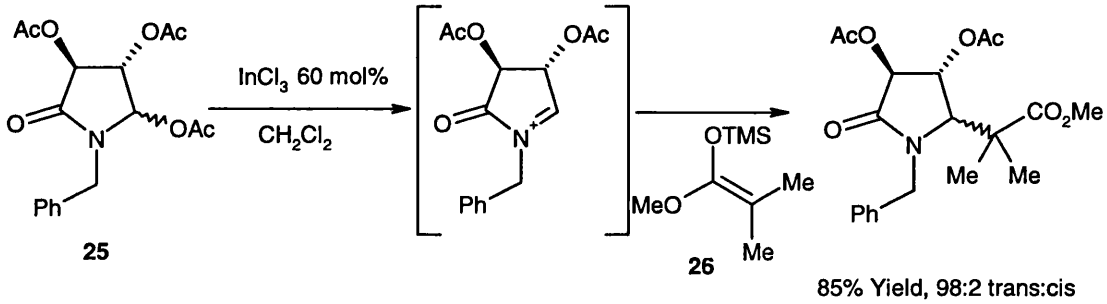
Scheme 20

α-Amino nitriles are of considerable interest, particularly in the synthesis of α-amino acids. In an excellent modification to the Streker reaction, Ranu and co-workers showed indium trichloride catalyses the one-pot three component coupling of a carbonyl compound, amine and potassium cyanide (Scheme 21).[35] Aromatic, aliphatic and heterocyclic aldehydes react smoothly at room temperature, whilst only cyclic ketones produce satisfactory results and require elevated temperatures.



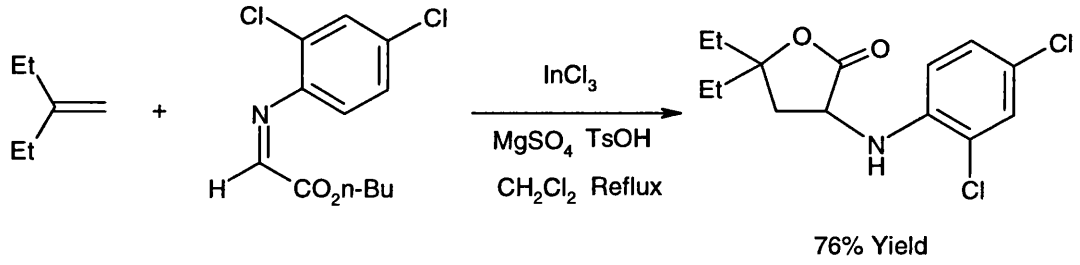
Scheme 21

Russowsky and co-workers showed that indium trichloride catalyses the addition of carbon nucleophiles to aromatic aldimines and cyclic *N*-acyliminium ions.[36] $InCl_3$ (60 mol%) is able to promote the reaction of *N*-acyliminium ions (generated from precursors **25**) silyl enolates (**26**) or allyltrimethylsilane (Scheme 22), generating 5-substituted lactams in reasonable to good yields. The aqueous media protocol described by Loh[32] cannot be employed due to preferential attack of the iminium ion by water affording 5-hydroxylactams.



Scheme 22

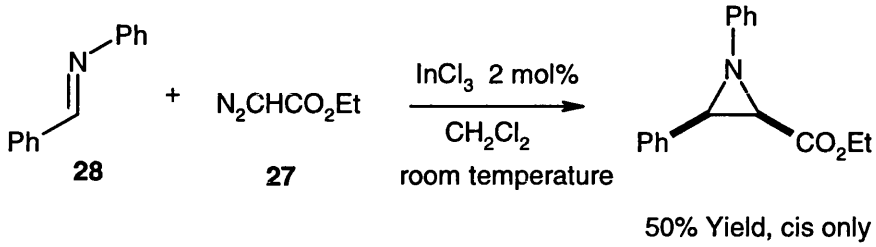
The synthesis of α-amino-γ-lactones can be achieved by an indium trichloride-mediated three-component reaction of alkenes, glyoxylates and amines.[37] In the presence of stoichiometric $InCl_3$, toluenesulfonic acid and magnesium sulfate, 1,1-dialkyl ethylenes undergo a [3+2] cyclisation with glyoxylate-derived imines (Scheme 23). Both cyclic and acyclic alkenes worked well but mono-substituted alkenes did not give the desired cyclisation product. The best yields were obtained using anilines bearing electron-withdrawing groups – aniline gave just 10% yield. Reducing the amount of $InCl_3$ resulted in much reduced yields.



Scheme 23

Indium trichloride catalysed reactions of ethyl diazoacetate with aldimines give aziridine carboxylates under mild conditions and low catalyst loading.[38] $InCl_3$ (2 mol%) catalyses the carbene insertion of α-diazoacetate (**27**) with aldimine (**28**) with

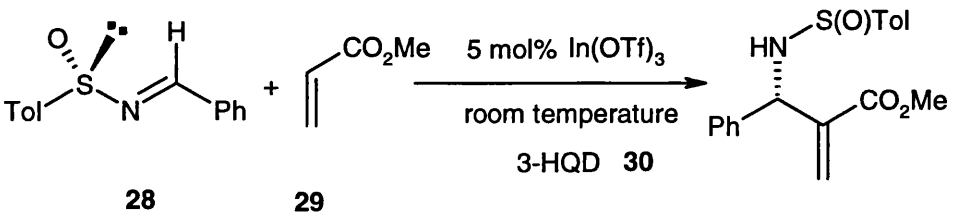
excellent *cis* selectivity albeit with moderate yield (Scheme 24). The best results were limited to aldimines derived from electron deficient aromatic aldehydes.



Scheme 24

The Bayliss-Hillman reaction is commonly used for the coupling of Michael acceptors with aldehydes to give β-hydroxy-α-methylene esters/ketones/nitriles. The use of imines in place of aldehydes provides entry to the corresponding β-amino products. Examples of the asymmetric Bayliss-Hillman reaction with imines are very rare. Aggarwal and co-workers[39] have shown that 10 mol% of indium triflate with 1 eq 3-hydroxyquinuclidine catalyses the reaction of methyl acrylate with enantiomerically pure *N*-sulfinimines in an asymmetric Bayliss-Hillman reaction.

Being much less electrophilic than the corresponding *N*-tosyl imines, the Bayliss-Hillman reaction of *N-p*-toluenesulfinimines were relatively low yielding (23 %, 7days, rt). However, the presence of 5 mol% $In(OTf)_3$ catalysed the reaction of sulfinimine **28** with methacrylate **29** in the presence of 3-hydroxyquinuclidine **30** in high yield and excellent d.e. (Scheme 25). Higher diastereoselectivity was observed in the reaction of *N-tert*-butanesulfinimines however the yields were much poorer.



28 29

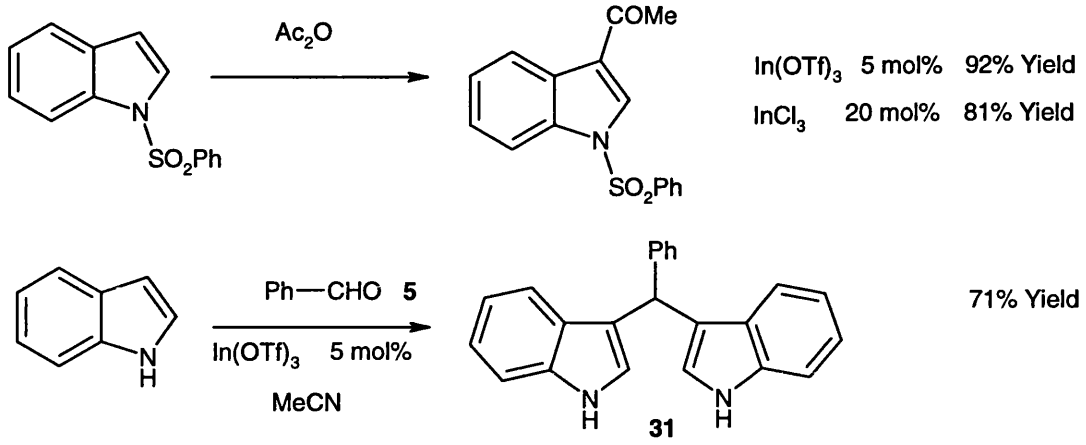
89% Yield, 64% d.e.

Scheme 25

Friedel-Crafts –type electrophilic aromatic substitution reactions constitute one of the most important classes of reactions in organic chemistry. Such reactions are traditionally promoted by stoichiometric amounts of Lewis acid, presenting purification and waste problems, particularly when carried out on an industrial scale.

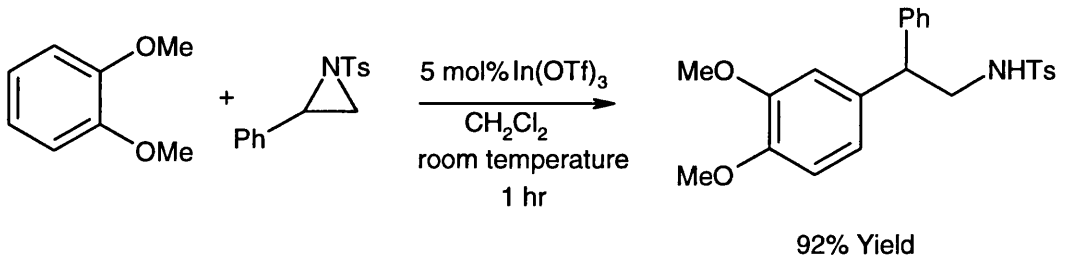
Perumal and Nagarajan showed that sub-stoichiometric amounts of indium(III) complexes promote the acylation of indoles under mild conditions and with short reaction times.[40] Both indium chloride (20 mol%) and indium triflate (5 mol%) are excellent catalysts for the acylation of indoles and *N*-protected indoles to their 3-acetylindole derivatives (Scheme 26).

Indium triflate also catalyses the reaction of indole with substituted benzaldehydes to afford bis-indolylmethanes. Scheme 26 shows the reaction of benzaldehyde **5** with indole proceeds in good yield in the presence of 5 mol% indium triflate to give bis-indolylmethane **31**.



Scheme 26

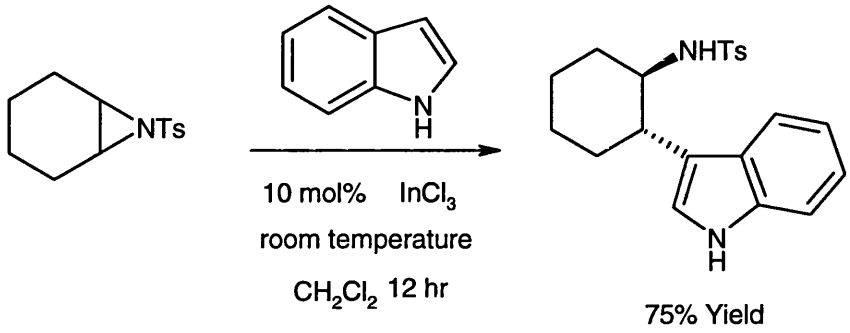
Arenes react smoothly with aziridines in the presence of a sub-stoichiometric amount of indium triflate (5 mol%).[41] Styrene *N*-tosyl aziridine underwent cleavage by arenes with attack coming primarily at the benzylic position (Scheme 27). Activated arenes gave the ring-opened products in excellent yields and short reaction time. Unactivated arenes also reacted well with aziridines in the presence of 10 mol% $In(OTf)_3$, although reaction times were comparatively longer.



Scheme 27

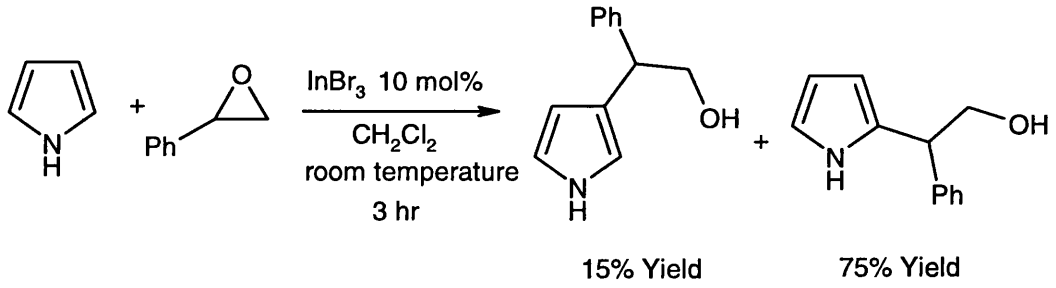
The use of 10 mol% $InCl_3$ allows the ring opening of aziridines by heteroaromatics. Yadav and co-workers[42] showed that indole, furan and thiophene react smoothly to give the 3-alkylated product, whilst pyrrole gives a mixture of 2- and 3-alkylated

pyrrole derivatives. When employing styrene-derived aziridines attack occurs primarily at the benzylic position. (Scheme 28).



Scheme 28

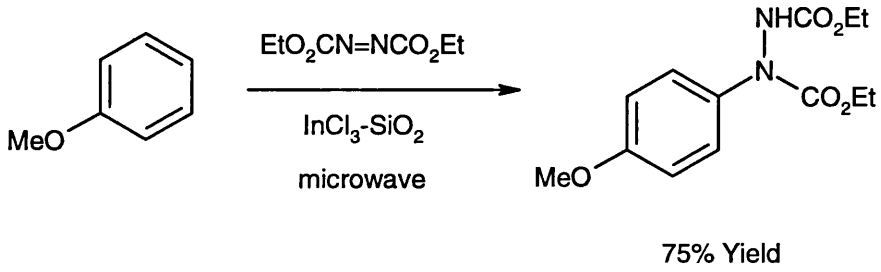
$InBr_3$ (10 mol%) catalyses the ring opening of epoxides with pyrrole to give 2- and 3-alkylated pyrroles in high yield under very mild conditions (rt, 2-5 hours).[43] Aryl oxiranes underwent cleavage by pyrrole with preferental attack at the benzylic position, glycidyl aryl ethers and alkyl oxiranes underwent cleavage with preferential attack at the terminal position. (Scheme 29).



Scheme 29

The Yadav group have also published an unusual electrophilic aromatic amination reaction catalysed by silica gel impregnated with indium chloride.[44] Under solvent-free microwave conditions, elecron-rich arenes reacted rapidly with

diethylazodicarboxylate (DEAD) to afford *para*-substituted aryl hydrazides in high yield (Scheme 30). Conventional heating (refluxing dichloroethane) also gave the desired amination products although reaction times were very much longer (8-22 hours vs 2-6 minutes). The catalyst ($InCl_3$-SiO_2) was prepared by adding silica gel to a solution of $InCl_3$ in acetonitrile followed by evaporation of the solvent.

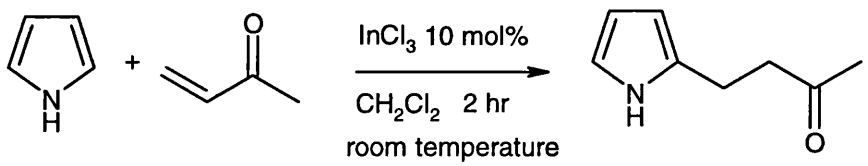


75% Yield

Scheme 30

Heterocycles such as pyrrole and indole are of great interest because of the great number of their derivatives occur in nature and possess a variety of biological activites. The derivatisation of such heterocycles remains difficult due to their acid sensitivity. Yadav and co-workers have show that indium chloride is an excellent catalyst for the addition of pyrroles[45] and indoles[46] to electron-deficient olefins.

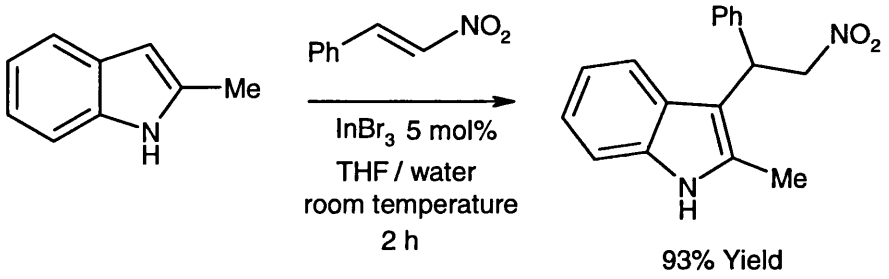
The reactions proceeded smoothly at ambient temperature with 10 mol% $InCl_3$ and there is no formation of side products such as dimers and trimers that are commonly observed under the influence of strong acids (Scheme 31).



85% Yield

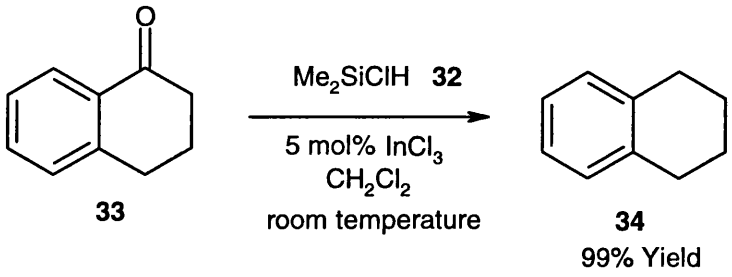
Scheme 31

An Italian group reported the indium bromide catalysed addition of indoles to nitroalkenes in aqueous media (9:1 H_2O:THF).[47] The protocol was effective for the addition of several electron-rich indoles and even indoles bearing electron-withdrawing groups. Consecutive reactions were carried out using $InBr_3$ recycled from the aqueous layer with no significant loss of activity (Scheme 32).



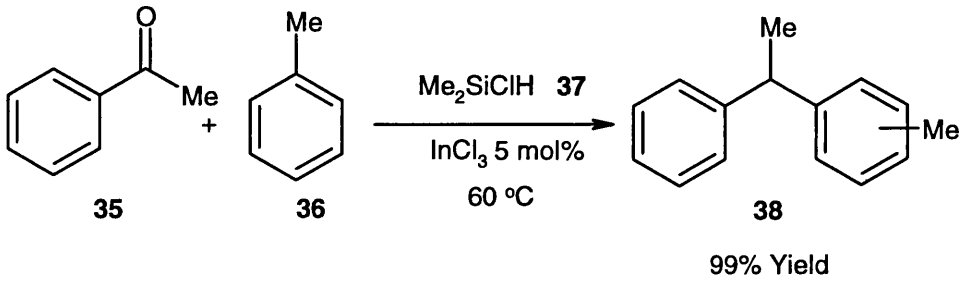
Scheme 32

The combination of chlorodimethylsilane **32** and an indium catalyst is extremely effective for reductive deoxygenation processes.[48] An illustration of the utility of this method is in the deoxygenation of tetralone **33**, the product **34** being obtained in quantitative yield. Although the indium(III) chloride catalysed protocol is depicted in Scheme 33, several indium sources proved to be effective.



Scheme 33

The same catalytic combination proved equally effective in the reductive Friedel-Crafts alkylation of aromatics with ketones or aldehydes (Scheme 34).[49] The reaction of acetophenone **35** with toluene **36** in the presence of chlorodimethylsilane **37** and sub-stoichiometric indium chloride furnished the reduced product **38** in quantitative yield as a mixture of regioisomers (predominantly *para*).

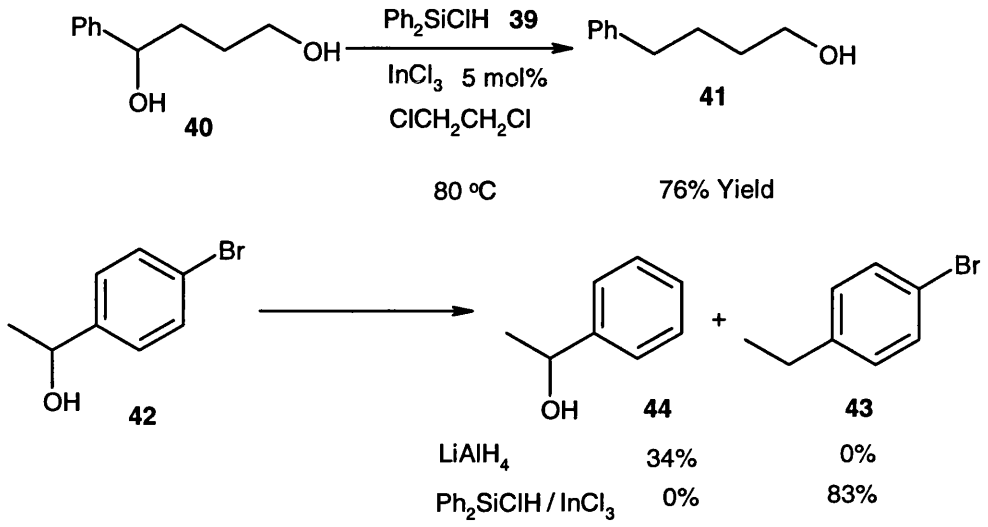


Scheme 34

The direct reduction of alcohols or carbonyls to alkanes is a difficult transformation with few examples reported. Nickel-catalysed hydrogenation requires high temperature and pressure (250 °C, 150 atm), whilst only alcohols that generate stable carbo cations are reduced using strong acidic media.

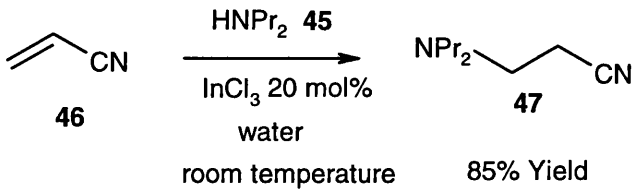
The use of chlorodimethylsilane and indium trichloride allows the reduction of only benzylic alcohols to alkanes. In an improved methodology, Baba and co-workers reported that the use of chlorodiphenylsilane **39** as a hydride source allows a far wider variety of benzylic, secondary or tertiary alcohols to be chemoselectively reduced to alkanes.[50] Treatment of diol **40** with the reducing system resulted in reduction of the secondary alcohol only and the primary alcohol **41** was obtained on work-up with Bu_4NF (Scheme 35). High chemoselectivity for the hydroxyl group in multifunctional compounds is demonstrated in the reduction of *p*-bromophenethylalcohol **42** to bromo

compound **43** in good yield. Standard reducing conditions using $LiAlH_4$ results in debromination to give the alcohol **44**.



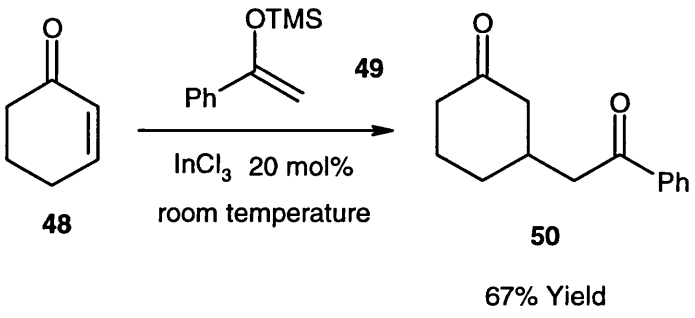
Scheme 35

A sub-stoichiometric amount of indium trichloride catalyses the Michael reaction between amines and α,β-ethylenic compounds in water and under mild conditions.[51] Thus, in the presence of 20 mol% $InCl_3$ the reaction of dipropylamine **45** with acryonitrile **46** proceeds in high yield to give product **47** (Scheme 36). The catalyst can be recovered from the aqueous phase and reused without loss of activity.



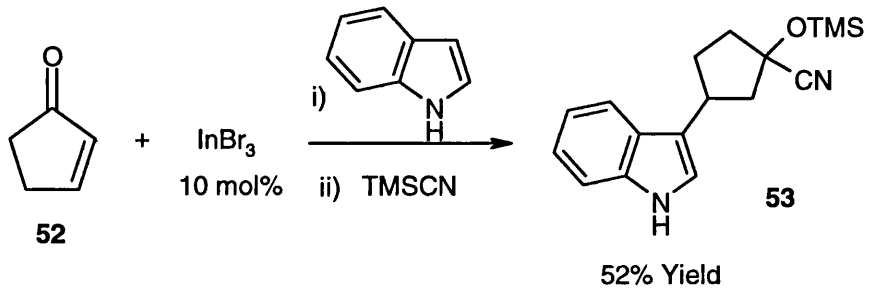
Scheme 36

Under solvent-free conditions, indium trichloride also catalyses the Michael reaction of silyl enol ethers with enones and alkenoates.[52] This is shown in Scheme 37, where cyclohex-2-enone **48** reacts with silyl enol ether **49** to give the Michael product **50** in good yield. A range of α,β-unsaturated ketones and esters, including acid-sensitive substrates such as methyl vinyl ketone (MVK), react in moderate to good yield. The catalyst can be recovered and reused.



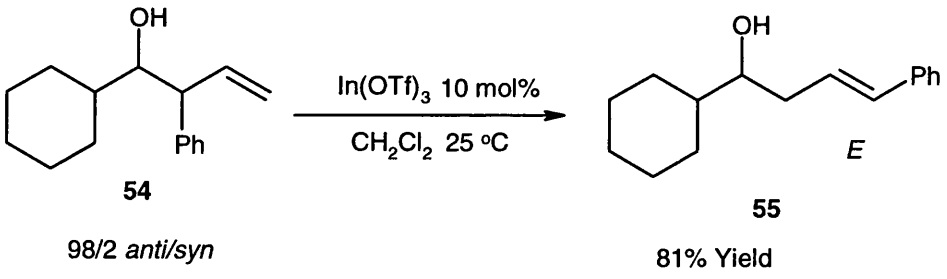
Scheme 37

Cozzi and co-workers have harnessed the remarkable tolerance of indium salts toward co-ordinating functional groups in a sequential one-pot 1,4- then 1,2-nucleophilic addition to enones.[53] The group demonstrated that indium tribromide catalyses the 1,4 conjugate addition of indoles and thiols to α,β-unsaturated ketones under mild conditions. In addition, subsequent 1,2 addition of TMSCN to the β-substituted ketones can be carried out in one pot. Thus, cyclopentenone **51** undergoes 1,4 addition of indole and subsequent 1,2 addition of TMSCN, to give product **52** (Scheme 38).



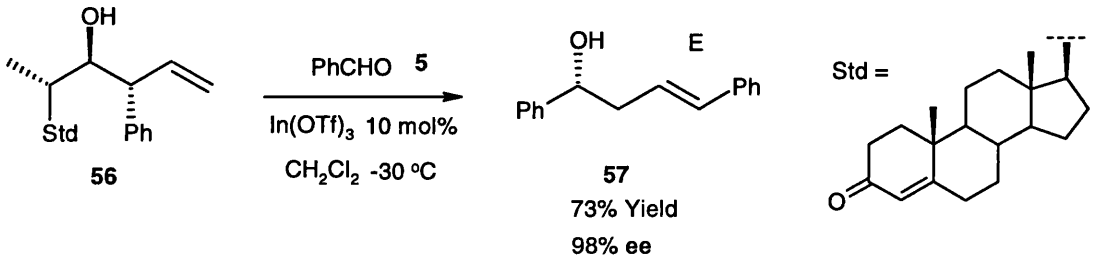
Scheme 38

The allylation of carbonyl compounds and the carbonyl-ene reaction offer ready access to synthetically useful homoallylic alcohols. However, both these reactions produce predominantly γ-adducts. Loh and co-workers reported the indium triflate catalysed conversion of branched homoallylic alcohols to the thermodynamically preferred linear regioisomers.[54] Under the reaction conditions, branched homoallylic alcohol **54** is converted to the linear product **55** in good yield (Scheme 39). A correlation between the relative stereochemistry of the substrate and the geometry of the double bond in the product was observed, with *syn* substrates leading to *Z* products and *anti* substrates leading to *E* products.



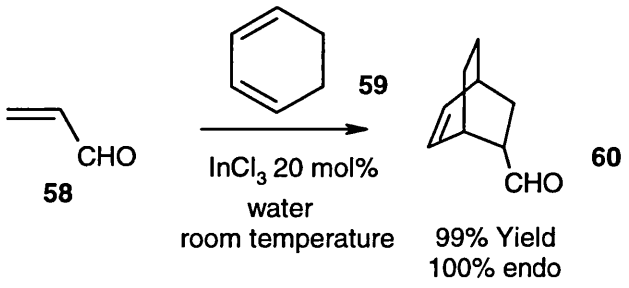
Scheme 39

The Loh group reported a homoallylic sterol/indium(III) Lewis acid reagent system for the enantioselective and α-regioselective allylation of aldehydes.[55] Allyl transfer from γ-adduct homoallylic sterol **56** to benzaldehyde **5** to give the α adduct **57** in good yield, excellent ee and E configuration of the double bond (Scheme 40).



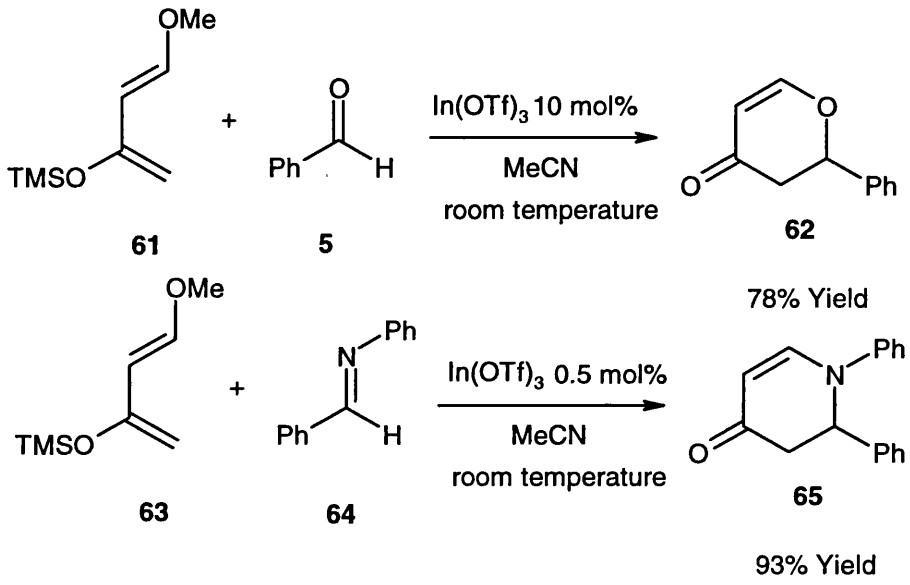
Scheme 40

The Diels-Alder reaction is known to show increased reactivity rates in water, especially when catalysed by a Lewis acid. Loh and co-workers showed that indium trichloride catalyses the Diels-Alder reaction between dienes and dienophiles under aqueous conditions.[56] Acrylaldehyde **58** reacts with cyclohexadiene **59** to afford the cycloaddition product **60** in excellent yield (Scheme 41).



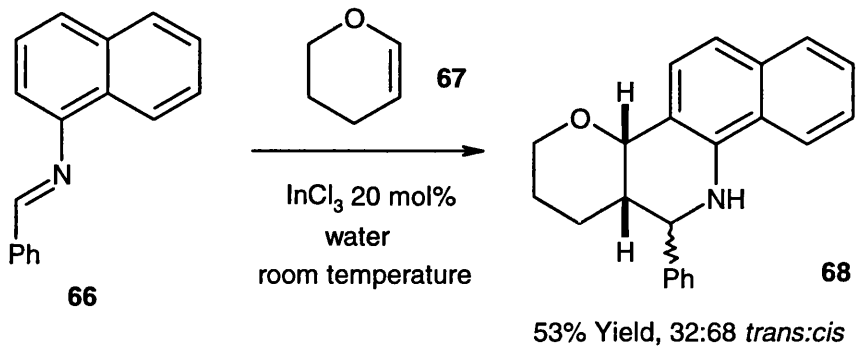
Scheme 41

The Frost group has demonstrated the use of indium triflate as a catalyst for hetero Diels-Alder reactions.[57] In the presence of 10 mol% indium triflate, benzaldehyde **5** reacts with Danishefsky's diene **61** to give the cycloaddition product **62**. Just 0.5 mol% $In(OTf)_3$ is required to catalyse the imino Diels-Alder reaction of imine **63** and diene **64**, furnishing **65** in excellent yield. A three component coupling of aldehyde, amine and diene is also reported.



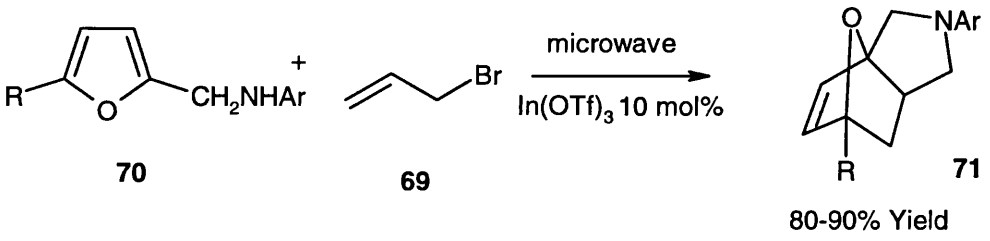
Scheme 42

Perumal and co-workers have utilised indium trichloride in the hetero Diels–Alder reaction of hetero dienes derived from aromatic amines. The reaction of Schiff's bases with cyclopentadiene, cyclohexen-2-one and cyclohepten-2-one results in rapid synthesis of cyclopentaquinolines, azabicyclooctanones and azabicyclononanones respectively. [58] Thus phenanthridine derivative **68** is formed by the indium trichloride catalysed reaction of **66** and **67** (Scheme 43).[59] Perumal's group also showed indium triflate can be employed to catalyse the imino Diels-Alder reaction of indolylimine with cyclopentadiene give indolylquinolone.[40]



Scheme 43

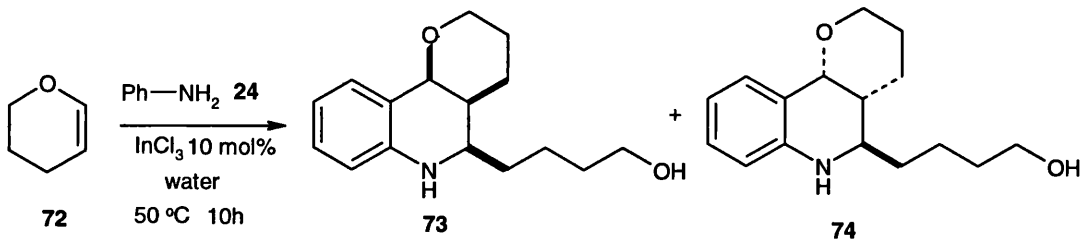
Indium triflate catalyses the intramolecular Diels-Alder reaction of furans in aqueous media under microwave irradiation.[60] In a one-pot procedure, allyl bromide **69** reacts with (2-furfuryl)anilines **70** in the presence of 10 mol% indium triflate, giving the intramolecular Diels-Alder products **71** in good to excellent yield, in very short reaction times (Scheme 44). Under thermal conditions, yields of 40-45% are obtained. Such products allow access to indole derivatives through cleavage of the epoxy bridge and aromatization.



Scheme 44

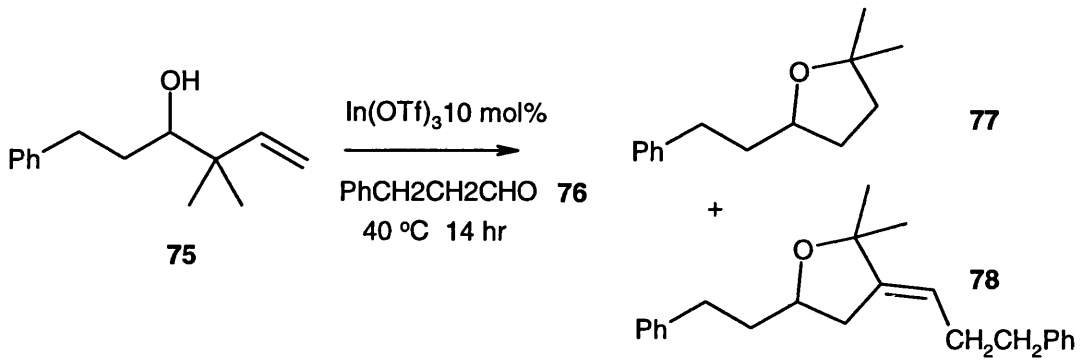
The aza-Diels-Alder reaction of *N*-Aryl imines is a powerful tool in the synthesis of tetrahydroquinoline derivatives.[61] Li and Zhang reported the indium trichloride-catalysed aza-Diels-Alder reaction as part of a domino reaction of aromatic amines

with cyclic enol ethers. Under aqueous conditions, aniline **24** reacts with 3,4 dihydro-2*H*-pyran **72** in the presence of 10 mol% indium triflate, to generate tetrahydroquinoline derivatives **73** and **74** (Scheme 45). Anilines bearing electron-donating groups were found to be more reactive than ones bearing electron-withdrawing groups.



Scheme 45

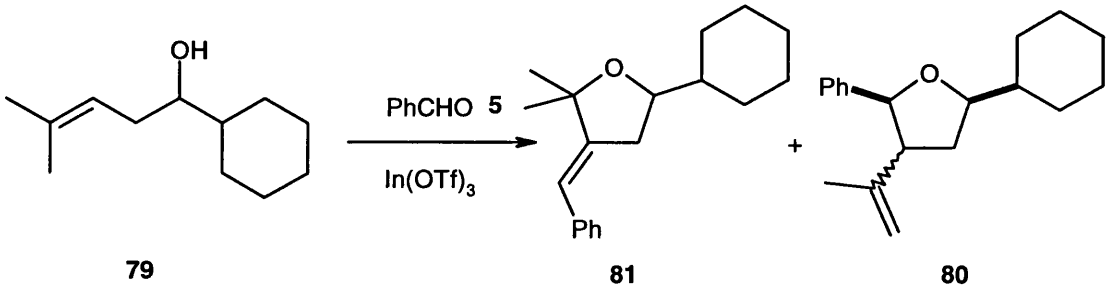
Indium triflate catalyses the formation of substituted tetrahydrofurans from 1,1-dimethyl-3-butenols.[62] A mixture of γ-adduct homoallylic alcohol **75** and the corresponding aldehyde **76** in the presence of sub-stoichiometric $In(OTf)_3$ (10-20 mol%) gave tetrahydrofurans **77** and **78**. When an equimolar amount of aldehyde was used tetrahydrofuran **78** was the major product, whilst a lower concentration of aldehyde gave increased amounts of tetrahydrofuran **77** (scheme 46). The mechanism is believed to consist of a 2-oxonia [3,3] sigmatropic rearrangement of the γ-adduct homoallylic alcohol to give the α-adduct which cyclises giving either **77** or **78**.



Aldehyde eq	Yield % (77:78)
0.1	56 (70:30)
1.0	60 (3:97)

Scheme 46

An array of multi-substituted tetrahydrofurans and tetrahydropyrans can be prepared through the indium triflate catalysed (3,5) oxonium-ene type cyclisation.[63] At 0 °C homoallylic alcohol **79** and aldehyde **5** undergo cyclisation to give tetrahydrofuran **80**. However, when the reaction was carried out at 40 °C, cyclisation product **81** is formed (Scheme 47).

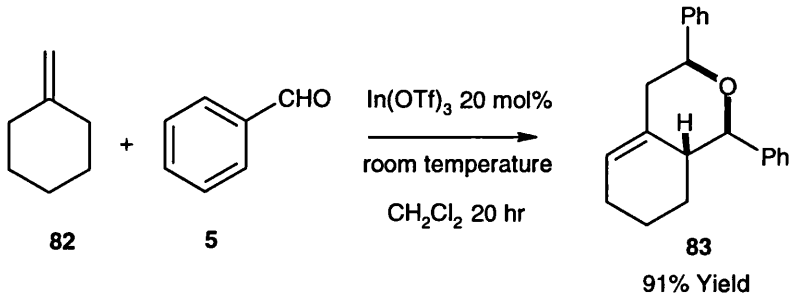


Temperature	Yield %
0 C	72 (**80**)
40 C	97 (**81**)

Scheme 47

Indium triflate catalyses the formation of tetrahydropyran rings through the self-tandem carbonyl-ene, intramolecular (2,5) oxonium-ene cyclisation of aldehydes and methylene cyclohexane.[64] Aldehyde **5** and methylenecyclohexane **82** react to give

homoallylic alcohols. Subsequent 2,5 oxonium-ene cyclisation involving a further molecule of aldehyde affords the tetrahydropyran **83** in very good yield and excellent diasteroselectivities, favouring the 2,3 *anti*, 2,6 *syn* isomers (Scheme 48). The 2,5 oxonium-ene cyclisation of preformed homoallylic alcohols also proceeds smoothly in the presence of indium triflate affording tetrahydropyrans in good yield.



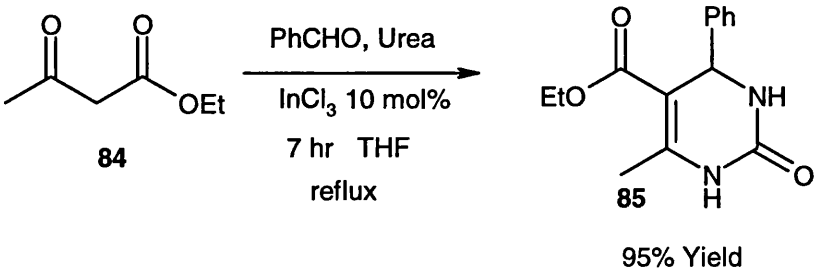
82 **5** **83**

91% Yield

Scheme 48

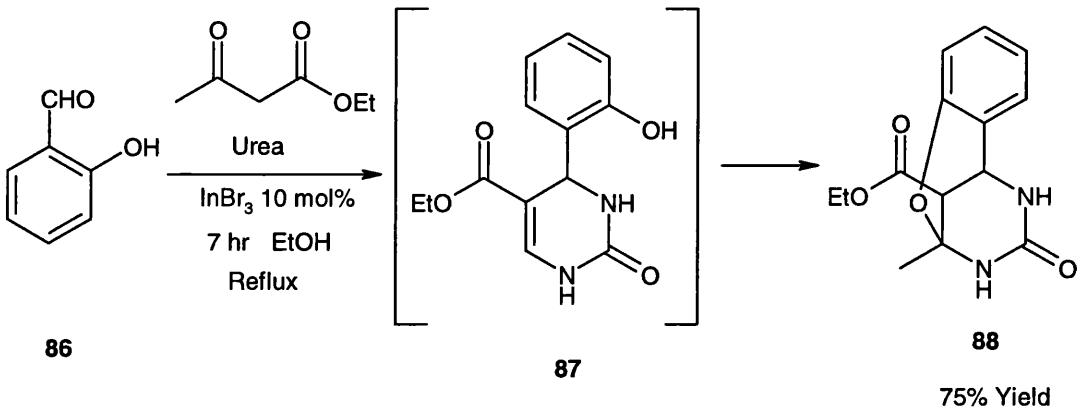
Dihydropyrimidinones have attracted considerable interest because of their interesting pharmacological properties. The Biginelli reaction, catalysed by HCl, involves a one-pot condensation of β-dicarbonyl compound, an aldehyde and urea (or thiourea) to give the desired dihydropyrimidinone, however yields are often low.

Ranu and co-workers reported that indium trichloride is an excellent catalyst for the Biginelli reaction.[65] Both β-keto esters and β-diketones participated in this reaction readily. Aromatic, aliphatic and heterocyclic aldehydes undergo cyclisation and both urea and thiourea react readily. On reaction of ethylacetoacetate **84**, benzaldehyde and urea at reflux in THF in the presence of $InCl_3$ (10 mol%), dihydropyrimidinone **85** is formed in excellent yield (Scheme 49).



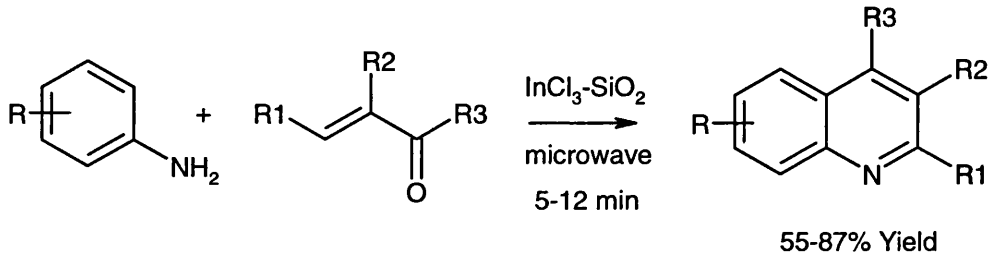
Scheme 49

Peppe and co-workers showed that indium tribromide is also an effective catalyst for the Biginelli reaction.[66] The use of $InBr_3$ means that anhydrous conditions are not necessary (in fact, the reactions are carried out in 95% EtOH) and the catalyst can be re-used without loss of activity. A range of β-ketoesters, aldehydes (including formaldehyde) and urea (or thiourea) undergo Biginelli condensation to give the dihydropyrimidinones in good to excellent yield. Interestingly, when salicylaldehyde **86** is used, diazatricyclic compound **88** is formed, following isomerisation of the product **87** (Scheme 50).



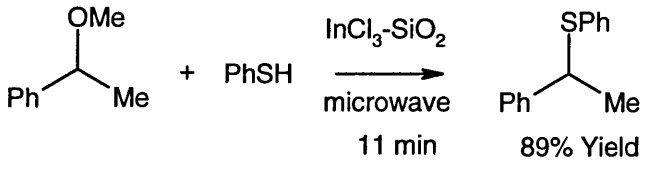
Scheme 50

The Skraup synthesis of quinolines requires a large amount of sulfuric acid, high temperatures and is often a violent reaction. Ranu and co-workers have demonstrated that $InCl_3$-SiO_2 catalyses the one-pot synthesis of 4-alkyl quinolines from anilines and alkyl vinyl ketones under microwave irradiation.[67] A range of anilines and alkyl vinyl ketones react to give substituted quinolines in good yield in short reaction times (5-12 min) (Scheme 51). $InCl_3$ alone proves an inefficient catalyst, whilst conventional heating results in considerable polymerisation.



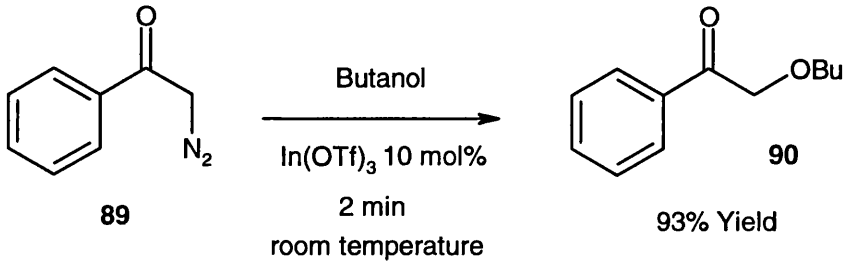
Scheme 51

Cyclic and open-chain benzylic ethers undergo an unusual cleavage by thiophenol on the surface of silica gel impregnated with indium trichloride.[68] Under microwave irradiation, cyclic ethers are cleaved to the corresponding dithioethers and benzylic ethers are cleaved to the corresponding monothioethers (Scheme 52). Dialkyl or aryl alkyl ethers are inert to the reaction conditions.



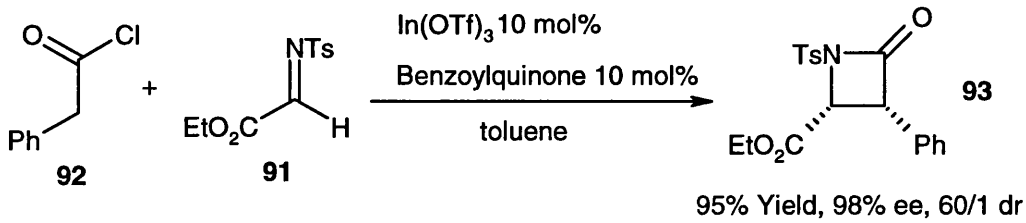
Scheme 52

Muthusamy and co-workers reported the indium triflate catalysed OH insertion reaction of α-diazo ketones.[69] In the presence of 10 mol% $In(OTf)_3$, a range of alcohols and thiols decomposed a variety of aromatic and aliphatic diazo compounds affording the respective α-alkoxy ketones under mild conditions. Thus, diazoacetophenone **89** in butanol reacts to give alkoxy ketone **90** in excellent yield.



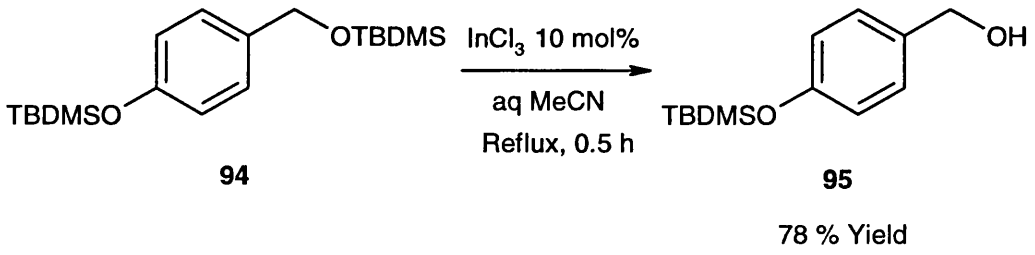
Scheme 53

The Lectka group has published a catalytic, asymmetric synthesis of β-lactams using a bifunctional catalyst system consisting of a chiral nucleophile and indium triflate.[70] Previous work has shown that nucleophilic ketenes react with electrophilic imines in the presence of a chiral nucleophile (typically benzoylquinone) to give β-lactams in high enantioselectivity but only moderate yield. Indium triflate was the best overall Lewis acid co-catalyst for benzoylquinone for promoting the reaction of *N*-tosyl imine **91** with ketene precursor, phenylacetyl chloride **92** forming β-lactam **93** in excellent yield (Scheme 54). High enantioselectivity was achieved (>95%) and the inclusion of catalyst increased the yield from 40-60% to 92-98%.



Scheme 54

Indium trichloride catalyses the cleavage of alkyl *t*-butyldimethylsilyl ethers.[71] The cleavage is affected in refluxing aqueous acetonitrile with high chemoselectivity. TBDPS ethers and aryl TBDMS ethers are unaffected by the reaction conditions. Thus, aromatic compound **94** is deprotected to alcohol **95** in good yield and high chemoselectivity (Scheme 55).



Scheme 55

1.3 Conclusion

Indium(III) salts have received considerable attention as Lewis acids in recent years. Their stability to co-ordinating atoms present in organic substrates makes them excellent catalysts in substoichiometric quantities. Stability in water allows aqueous recycling and the use of water as a reaction solvent.

CHAPTER 2

ACYLATION AND SULFONYLATION

2 Acylation and Sulfonylation

2.1 Acylation

Since the publication by Charles Friedel and James Mason Crafts in 1877, of a paper entitled "Sur une nouvelle méthode générale de synthèse d'hydrocarbures, d'acétones, etc" detailing the reaction of amylchloride with benzene in the presence of aluminium chloride,[72] the scope of what is called a Friedel-Crafts reaction has widened so as to make an exact definition difficult. Substitution, isomerization, elimination, cracking, polymerization and addition reactions under the effect of Lewis acids are all referred to as Friedel-Crafts reactions. However, to generalise, a Friedel-Crafts reaction involves the following components:[73]

a) The substance to be substituted (e.g. an arene, olefin)

b) A reagent to provide the substituent (e.g. acyl or alkyl halide)

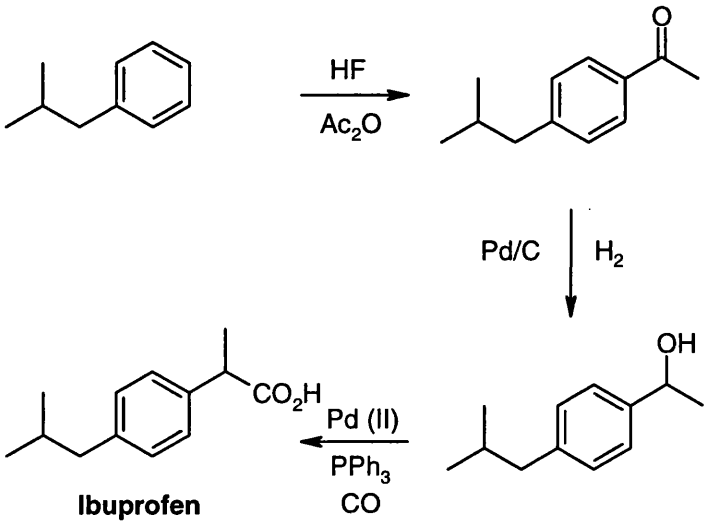
c) A catalyst, usually a Lewis or Brønsted acid

d) A solvent (this can be an excess reagent)

e) The substituted product

f) The by-product generated from the substituent donor.

The Friedel-Crafts acylation reaction is one of the oldest reactions for the preparation of ketones by carbon-carbon bond formation. The products are widely used commercially, for example, in the synthesis of anthraquinone dyes[73a] and pharmaceuticals such as anti-inflammatory drugs Naproxen and Ibuprofen[74] (Scheme 56), anti-cancer drug Tamoxifen[75] and anti-hyperlipemic Fenofibrate.[76]

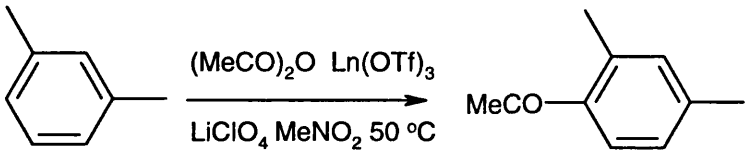


Scheme 56

Whilst the alkylation reaction proceeds in the presence of a sub-stoichiometric amount of Lewis acid such as $AlCl_3$ or BF_3, the acylation reaction requires more than a stoichiometric amount of Lewis acids due to coordination to the product ketones. This leads to an environmentally hostile process with gaseous effluents and mineral wastes. Some catalysts have been reported including $FeCl_3$, $ZnCl_2$,[77] zeolites[78] and $GaCl_3$-$AgClO_4$[79] but show activity only in the acylation of activated aromatics. Extension of $FeCl_3$ catalysis to unactivated aromatics has been achieved under microwave conditions.[80] Efficient Brønsted acid catalysts are known including superacidic systems[81] and sulfonic acids.[82]

Olah and co-workers reported the first use of metal triflates as catalysts for acylation.[83] Boron, aluminium and gallium triflates were shown to catalyse the benzoylation of toluene in up to 72% yield. However, 50 mol% of these highly sensitive catalysts is required.

Transition metal salts such as lanthanide, scandium and copper triflates[84] and triflamides[85] have been developed as catalysts for acylation reactions. Their stability in water enables their recycling through the aqueous phase on work up. Their catalytic activity is limited, however, to the acylation of activated aromatics. The addition of lithium perchlorate additive has been shown to enhance the efficacy of such catalysts (Scheme 57). Thus $Sc(OTf)_3$ (20 mol%) catalyses the acylation of *m*-xylene at 50 °C in a $MeNO_2$-$LiClO_4$ reaction mixture in good (82%) yield.[86] Systems involving $SbCl_5$,[87] $Hf(OTf)_3$,[88] $Ga(OTf)_3$ and $Sb(OTf)_3$[89] with lithium perchlorate have exhibited superior activity to those of $Sc(OTf)_3$.



$LiClO_4$ (equiv.)	Yield (%) (Ln = Sc[a])	Yield (%) (Ln = Yb[b])
0	12	0
0.8	28	17
1.0	36	22
2.0	51	38
6.0	82	83

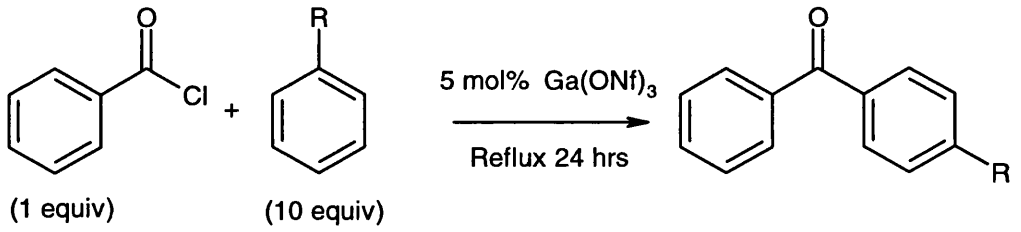
[a] Reaction time 1 h.
[b] Reaction time 4 h.

Scheme 57

The acylation of more demanding aromatic substrates (benzene, toluene and halobenzenes) has been achieved using a $Hf(OTf)_4$-TfOH system.[90] Dubac and co-workers revealed the strong activity of $Bi(OTf)_3$ for acylation reactions,[91] allowing the

acylation of activated aromatics and the benzoylation of deactivated aromatics. The latter process involves an exchange reaction with benzoyl chloride to generate the highly reactive benzoyl triflate *in situ*.[92]

During the course of our investigations, Kobayashi and co-workers published an improved Ga(III)-mediated acylation procedure. In the presence of a sub-stoichiometric amount of gallium nonafluorobutanesulfonate ($Ga(ONf)_3$), aromatics including unactivated aromatics such as fluorobenzene, chlorobenzene and dichlorobenzene reacted with benzoyl chlorides to give the corresponding ketones in high yield (Scheme 58).[93]



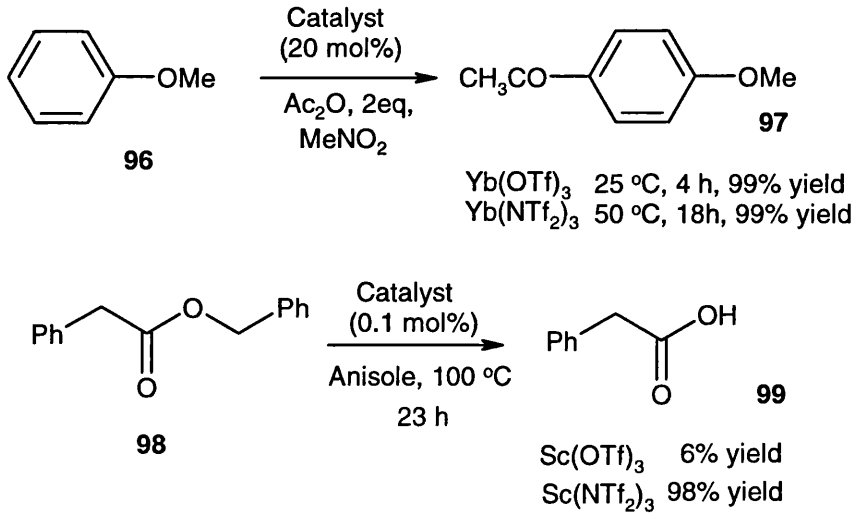
R	Yield (%)
H	90
Me	88
Cl	98
F	91

Scheme 58

The use of the CF_3SO_2 (Tf) group as an electron-withdrawing substituent on nitrogen substantially increases the acidity of an amine, imine or imide. Compounds such as

$CF_3SO_2NH_2$ and $CF_3SO_2N(H)Ph$ exhibit pK_a values of weak acids. Two sulfonyl groups on nitrogen drastically increase the acidity of the remaining proton, as shown by $(FSO_2)_2NH$,[94] $(RSO_2)_2NH$[95] (R = Ar) and bis(perfluoroalkylsulfonyl)imides $HN(SO_2R_f)_2$ (R_f= CF_3, C_2F_5 and C_4F_9).[96]

$HNTf_2$ is a good catalyst for C-C bond-forming reactions such as Friedel-Crafts, Mukaiyama, 1,2 additions and 1,4 additions.[97] Metal salts of $HNTf_2$ have been reported as effective Lewis acid catalysts for Diels-Alder,[98] acetylisation,[99] acetalisation,[100] debenzylation[101,102] and Friedel-Crafts[85] reactions. Metal triflamides, are, in general, much more effective Lewis acid catalysts than metal triflates, $M(OTf)_n$ (Scheme 59). Acylation of anisole **96** to the ketone **97** proceeds under much milder conditions when using $Yb(NTf_2)_3$ compared with $Yb(OTf)_3$. $Sc(NTf_2)_3$ is a far superior catalyst than $Sc(OTf)_3$ in the deprotection of benzyl ester **98** to acid **99**.



Scheme 59

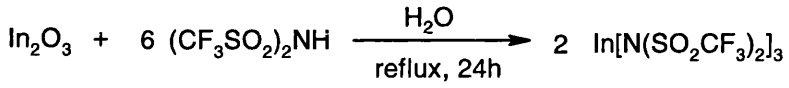
2.1.1 Indium(III) Catalysed Acylation of Anisole

Indium(III) salts have attracted great attention as Lewis acid catalysts in many organic transformations (Chapter 1). Our group have achieved excellent results in the acylation of heteroatoms (alcohols, amines[7] and aldehydes[103]) and Diels-Alder reactions[57] when using indium(III) salts at low catalyst loadings (0.5-1 mol%). We envisaged extending the scope of In(III)-catalysed reactions to electrophilic aromatic substitution reactions allowing the functionalisation of aromatics whilst maintaining the mild conditions and low catalyst loadings we had previously employed.

In addition to using commercially available indium(III) salts we synthesised the new indium complex indium(III) triflamide, $In(NTf_2)_3$. We perceived that by changing the counterion on indium from triflate to triflamide (NTf_2^-), we would enhance the catalytic activity, whilst maintaining low catalyst loadings.

The new indium complex, $In(NTf_2)_3$, was easily prepared in high yield from indium oxide (In_2O_3) and bis(trifluoromethylsulfonyl)imide ($HNTf_2$). Thus, a suspension of indium oxide in water was treated with $HNTf_2$ and heated at reflux for 24 hours. On cooling the reaction mixture was filtered to remove any unreacted In_2O_3 and the aqueous solution was concentrated *in vacuo*. After drying under vacuum at 100 °C, $In(NTf_2)_3$ was recovered as a hygroscopic, white partially crystalline solid, in almost quantitative yield. The new complex was identified by a shift from δ –75.2 (Tf_2NH) to

δ –79.0 in the ^{19}F NMR and mass spectrum of M^- of 280 and 282 (Tf_2N^-). Crystals suitable for X-ray analysis were unable to be grown.

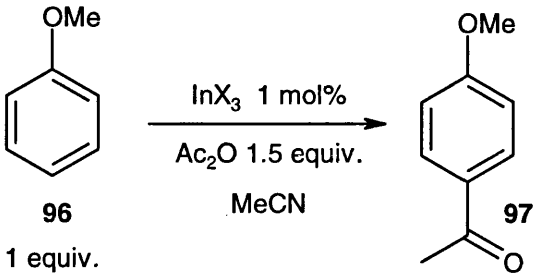


Scheme 60

Initial research was directed towards a screen of available Lewis acids and conditions in the acylation of activated aromatic anisole **96** (σ_p^+ = -0.76), and preliminary results are presented in Table 2.1. To begin with, the conditions developed for the acylation for heteroatoms,[7] namely 1 mol% catalyst, 1.5 equivalents acetic anhydride, in acetonitrile for 1 hour at room temperature were employed. Aqueous work-up and ^1H NMR of the crude product showed very little of the acylated product was formed (entry 1). Elevated temperature, however, increased the yield of 4-methoxyacetophenone when using $In(OTf)_3$ (entries 3-5). The product **97** was identified in the ^1H NMR by the appearance of a singlet at δ2.58, representing the acyl group, and two multiplets at δ6.93 and δ7.92.

The efficacy of the indium(III) salt used appears to depend on the counter ion (entries 3, 7-9). The use of isopropenyl acetate as an acyl donor was investigated as it produces acetone as a neutral by-product;[104] however, under these conditions no reaction was observed (entries 2 and 6). In all successful reactions, aqueous work-up and column chromatography afforded the product ketone with exclusive *para* selectivity.

Table 2.1 Yields of 4-methoxyacetophenone with variation of catalyst, reaction time and temperature



96
1 equiv.

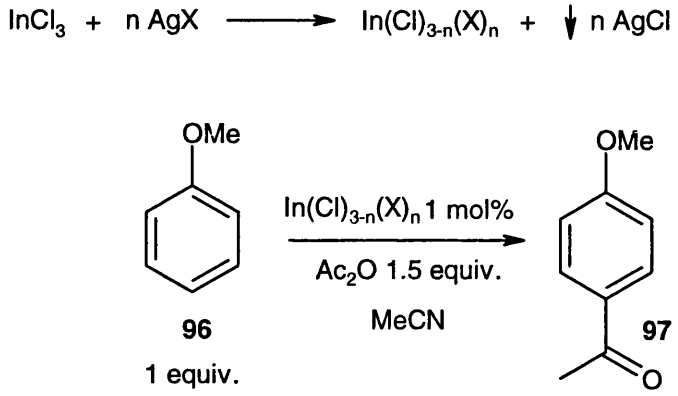
97

Entry	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	$In(OTf)_3$	25	1	4
2	$In(OTf)_3$	25	1	0*
3	$In(OTf)_3$	50	1	28
4	$In(OTf)_3$	50	6	58
5	$In(OTf)_3$	80	1	90
6	$In(OTf)_3$	50	1	0*
7	$InCl_3$	50	1	26
8	$In(acac)_3$	50	1	0
9	In_2O_3	50	1	0

*isopropenylacetate used in place of acetic anhydride

Having observed marked counter-ion effect in the indium(III) catalysed acylation, a variety of indium(III) complexes were prepared from metathesis reactions of indium trichloride and silver salts containing weakly co-ordinating anions. The complexes were then screened in the acylation of anisole (Table 2.2).

Table 2.2 Effect of counter ions on indium(III) catalysed acylation of anisole[a]



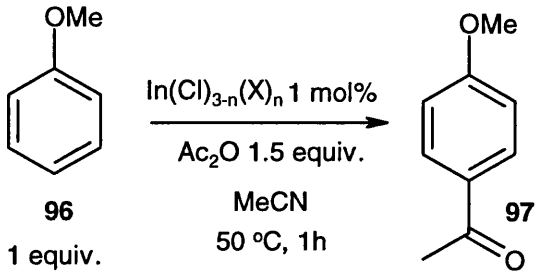
Entry	Silver salt added[b]	Yield (%)
1	None	26
2	$AgClO_4$ (3)	82
3[c]	$AgClO_4$ (3)	0
4	$AgBF_4$ (3)	55
5	$AgSbF_6$ (3)	7

[a] Experimental conditions: Acetic anhydride/anisole = 1.5:1, 1 mol% $InCl_3$, MeCN, 50 °C, 1 h.
[b] Mol% silver salt in brackets.
[c] Reaction at ambient temperature.

An initial screen of counter ions revealed perchlorate to be the most effective (entries 1, 2, 4 and 5). It was noted, however, that on addition of acetic anhydride to the indium and silver salts, the suspension of AgCl dissolved. With both metal salts in solution, a mixture of indium complexes, containing none, one, two or three ligands, could be present in the reaction mixture.

In an effort to delineate the active catalyst present when using $InCl_3$ with 3 equivalents of $AgClO_4$, further catalyst systems were filtered *via* cannula transfer, following metathesis (Table 2.3). The optimum catalyst appears to be $InCl(ClO_4)_2$ (entry 2). Changing solvent from acetonitrile to nitromethane increases yield markedly (entries 5 and 6).

Table 2.3 Effect of counterion following filtration[a]

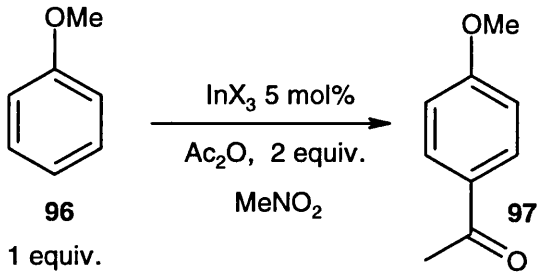


Entry	Silver salt added[b]	Yield (%)
1	$AgClO_4$ (1)	25
2	$AgClO_4$ (2)	80
3	$AgClO_4$ (3)	46
4	$AgClO_4$ (4)	52
5	AgOTf (1) + $AgClO_4$ (2)	52
6[c]	AgOTf (1) + $AgClO_4$ (2)	82

[a] Experimental conditions: Acetic anhydride/anisole = 1.5:1, 1 mol% $InCl_3$, MeCN, 50 °C, 1 h.
[b] Mol% silver salt in brackets.
[c] Nitromethane used as solvent.

The use of $In(NTf_2)_3$ in acylation reactions in place of $In(OTf)_3$ resulted in enhanced catalytic activity. Under mild conditions, $In(NTf_2)_3$ is a superior catalyst for the acylation of anisole (Table 2.4). This potent catalytic activity extends to the acylation of mesitylene, but toluene and chlorobenzene were unaffected by such mild conditions.

Table 2.4 Catalyst comparison in acylation[a]



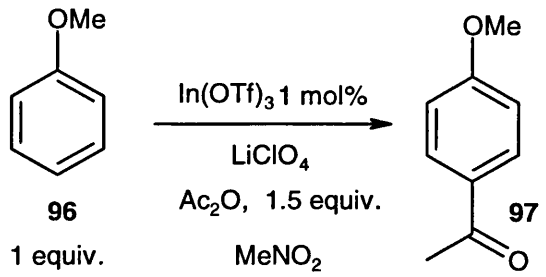
Catalyst	Time (h)	Temperature (°C)	Yield (%)
$In(OTf)_3$	4	25	66
$In(NTf_2)_3$	4	25	83
$In(OTf)_3$	1	50	76
$In(NTf_2)_3$	1	50	95
$In(NTf_2)_3$[b]	1	50	99
$In(NTf_2)_3$[c]	1	50	0
$In(NTf_2)_3$[d]	1	50	0

[a] Conditions: Ac_2O/anisole 2:1; 5 mol% catalyst.
[b] Mesitylene used as aromatic substrate.
[c] Toluene used as aromatic substrate.
[d] Chlorobenzene used as aromatic substrate.

Although good yields were achieved through the use of sub-stoichiometric mixed chloride-perchlorate indium complex, the tedious preparation of the catalyst and the problems associated with silver salts (cost and light sensitivity) demanded an alternative approach.

Having observed the efficacy of metal triflate-lithium perchlorate systems for acylation reactions,[86-89] we investigated the effect of lithium perchlorate additives to the indium(III) catalysed acylation of anisole (Table 2.5).

Table 2.5 Effect of $LiClO_4$ additives on the In(III) catalysed acylation of anisole[a]



Entry	Indium salt	$LiClO_4$ (mol%)	Yield (%)
1	$In(OTf)_3$	2	69
2	$In(OTf)_3$	4	79
3	$In(OTf)_3$	25	88
4	$In(OTf)_3$	100	96
5[b]	$In(OTf)_3$	100	99
6	$In(ClO_4)_3.8\ H_2O$	100	91

[a] Experimental conditions: Acetic anhydride/anisole = 1.5:1, 1 mol% InX_3, $MeNO_2$, 50 °C, 1 h.
[b] At ambient temperature for 40 h.

The addition of one equivalent of lithium perchlorate provided the most active system (entry 4), allowing excellent conversion under mild conditions and with short reaction time. The reaction proceeded at room temperature, although a longer reaction time was required (entry 5). It should be noted that, under these conditions, $LiClO_4$ alone did not catalyse the reaction.

After dilution of the reaction mixture with DCM and water, the aqueous phase can be evaporated under reduced pressure. The indium(III) and lithium salts were recovered as a white solid which can be recycled and used repeatedly without loss of activity (Table 2.6).

Table 2.6 Recycling indium(III) triflate and lithium perchlorate for the acylation of anisole with acetic anhydride

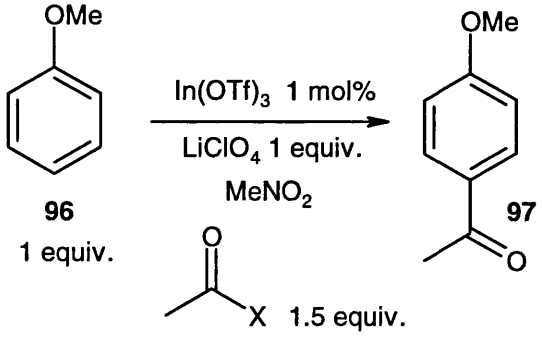
Run	Isolated yield (%)	Recovery of salts (%)
1	96	> 99
2	93	> 99
3	85	> 99

2.1.2 Acyl Donors

Whilst carboxylic anhydrides are one of the most reactive acyl sources, the use of anhydrides has two drawbacks: the relatively limited diversity of commercially available anhydrides when compared with carboxylic acids, and the acidic by-product. Acylation with acid halides derived from the parent acid solves the former problem, whilst a number of efficient acyl donors with neutral by-products have been developed, principally in the field of pH-dependant enzyme-catalysed reactions, which provide a solution to the latter.[104,105]

A number of acyl donors were screened using the optimised conditions for the acylation of anisole (Table 2.7). Acetic and propanoic anhydride results in high yields of the products **97** and 4-methoxypropanophenone **100** respectively.

Table 2.7 Effect of acyl donor on the acylation of anisole[a]

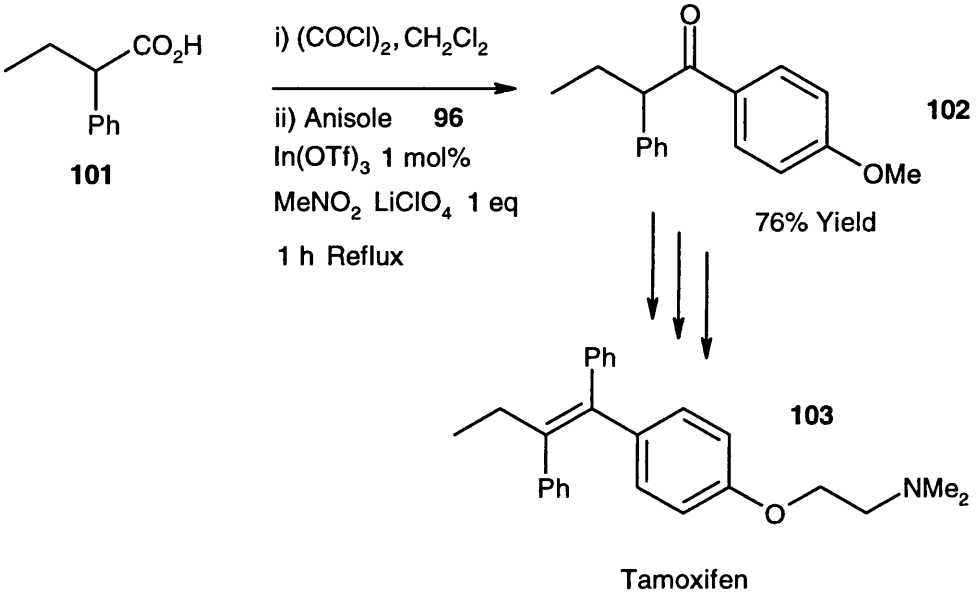


Entry	Acyl Donor	By-Product	Yield (%)
1	Acetic anhydride	Acetic acid	96
2	Propanoic anhydride	Propanoic acid	99
3	Acetyl chloride	HCl	42 (87)[b]
4	Isopropenyl acetate	Acetone	35 (76)[c]
5	Vinyl acetate	Acetaldehyde	0
6	Acetic acid	Water	0
7	1-cyclohexenyl acetate	Cyclohexanone	0

[a] Experimental conditions: Acyl donor/anisole = 1.5:1, $In(OTf)_3$ 1 mol%, $LiClO_4$ 100 mol%, $MeNO_2$, 50 °C, 1 h.
[b] Reflux.
[c] Isopropenyl acetate added dropwise over 1 hour.

Acetyl chloride and isopropenyl acetate provided the only viable alternative to carboxylic anhydrides. Slow addition of the isopropenyl acetate during the reaction resulted in a good yield and clean product (entry 4). By heating the reaction to reflux, the use of acetyl chloride provided a good yield of ketone (entry 3). A wide scope of ketones can be produced from carboxylic acids through conversion to the corresponding acid chloride followed by $In(OTf)_3$-$LiClO_4$ catalysed acylation.

This is illustrated in the $In(OTf)_3$-$LiClO_4$ catalysed Friedel-Crafts acylation of anisole **96** with the acid chloride generated from **101**, to give 1-(4-methoxyphenyl)-2-phenyl-butanone **102** in 76% yield over two steps from the corresponding acid. 1-(4-methoxyphenyl)-2-phenyl-butanone is an intermediate in the synthesis of anti-cancer agent Tamoxifen **103**.[106]



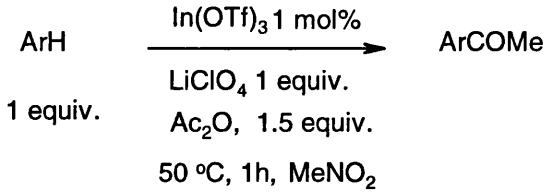
Scheme 61

2.1.3 Aromatic Substrates

The scope of the reaction with respect to the aromatic substrate was explored, using the optimised conditions (Table 2.3, entry 4). Activated aromatics anisole, mesitylene, *m*-xylene and furan were acylated smoothly in high yield (Table 2.6, entries 1-4). Toluene is a less activated aromatic ($\sigma_p^+ = -0.306$) and required harsher conditions (10 mol% $In(OTf)_3$, reflux), but 4-methylacetophenone is obtained in good yield in 1 hour

(Table 2.6, entry 5). No reaction was observed for chlorobenzene, a deactivated aromatic ($\sigma_p^+ = +0.112$) (Table 2.6, entry 6).

Table 2.6 $In(OTf)_3$-$LiClO_4$ Catalysed Friedel-Crafts Acylation[a]

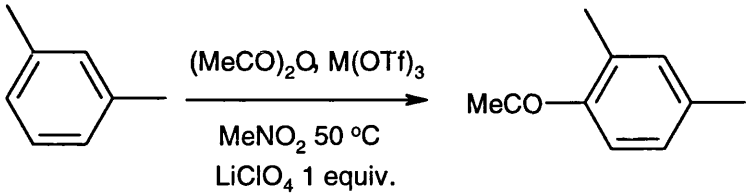


Entry	Substrate	Product[b] and Yield (%)
1	Anisole	**97**; 96
2	Mesitylene	**104**; 99
3	Furan	**105**; 99
4	*m*-Xylene	**106**; 90
5	Toluene	**107**; 0 (82)[c]
6	Chlorobenzene	**108**; 0

[a] Experimental conditions: Acetic anyhdride/aromatic = 1.5:1, $In(OTf)_3$ 1 mol%, $LiClO_4$ 100 mol%, $MeNO_2$, 50 °C, 1 h.
[b] Acylation products are 4-methoxyacetophenone (**97**), 2, 4, 6-trimethylacetophenone (**104**), 2-acetylfuran (**105**), 2, 4-dimethylacetophenone (**106**), 4-methylacetophenone (**107**), 4-chloroacetophenone (**108**).
[c] 10 mol% $In(OTf)_3$, reflux.

The catalytic acylating system we have developed compares favourably with the use of traditional stoichiometric Lewis acids. Low catalyst loadings (1 mol%) are used, and the catalyst system can be recycled through the aqueous phase, something incompatible with such Lewis acids as aluminium trichloride. The catalytic activity of $In(OTf)_3$ is also superior to a number of metal triflate catalysts, particularly those of

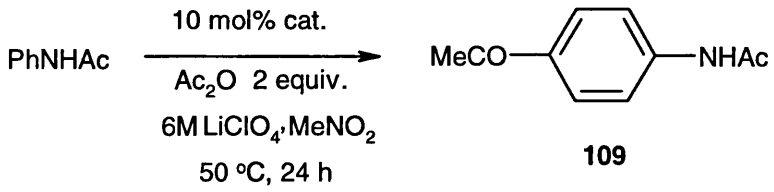
scandium, ytterbium and other lanthanide metals. As shown in Scheme 62, despite lower catalyst loading $In(OTf)_3$ is a superior catalyst in the acylation of *m*-xylene compared with scandium and ytterbium triflates.[86]



$M(OTf)_3$ (mol%)	Time (h)	Yield (%)
$In(OTf)_3$ (1)	1	90
$Sc(OTf)_3$ (20)	1	36
$Yb(OTf)_3$ (20)	4	22

Scheme 62

Following the publication of our own results on the acylation of aromatics with $In(OTf)_3$ and $LiClO_4$, Kobayashi and co-workers reported the use of gallium(III) salts in the Friedel-Crafts acylation of aniline derivatives.[107] A comparison of the catalytic activity of metal triflates in the acylation of acetamide was included in their work (Scheme 63). Our own results using indium triflate show it is the most efficacious catalyst that can be recycled through aqueous extraction (gallium triflate is water sensitive).



109

Catalyst	Yield (%)
$GaCl_3$	33
$Ga(OTf)_3$	93
$Ga(ONf)_3$	90
$In(OTf)_3$	74
$Sc(OTf)_3$	10
$Hf(OTf)_4$	44
$Sb(OTf)_3$	59
$Bi(OTf)_3$	59

Scheme 63

2.2 Benzoylation

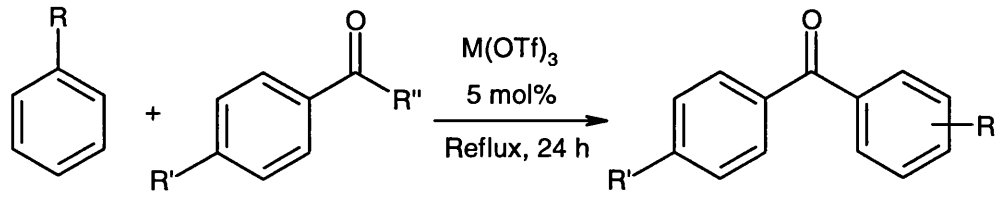
2.2.1 Indium(III) Catalysed Benzoylation

Whilst the catalytic activity of indium triflate – lithium perchlorate is high for activated aromatics, the inability of the catalyst system to facilitate the acylation of chlorobenzene, a deactivated aromatic, remained problematic. Previous work had shown that benzoyl chloride was the best acylating agent for reactions with inactivated substrates.[90-93] Thus, we investigated the use of indium triflate and indium triflamide as catalysts in Friedel-Crafts benzoylation reactions.

Aroyl chloride (1 equivalent) was treated with an indium(III) salt (5 mol%) in an excess of aromatic (10 equivalents) and heated to reflux for 24 hours (Table 2.7). As table 2.7 shows, $In(OTf)_3$ is an excellent catalyst. Activated aromatics are benzoylated in high yield (entries 1 and 3), and unactivated aromatics in good yield (entries 4 and 7). It is interesting to note that benzoic anhydride is a poor benzoylating agent for benzene (entry 6).

In a comparison with other metal triflates, scandium was totally ineffective for benzoylating benzene (entry 9) whilst only gallium triflate was more effective than indium (entry 11). The hierarchy of catalytic activity, $In(NTf_2)_3 > In(OTf)_3$, observed in the acylation of arenes, is maintained for the benzoylation of toluene (entry 2). However, for unactivated and deactivated (PhCl, $\sigma_p^+ = + 0.112$) aromatics, indium triflamide is a poor catalyst (entries 5 and 8), thus $In(OTf)_3$ is the catalyst of choice.

Table 2.7 Friedel-Crafts Benzoylation Reactions



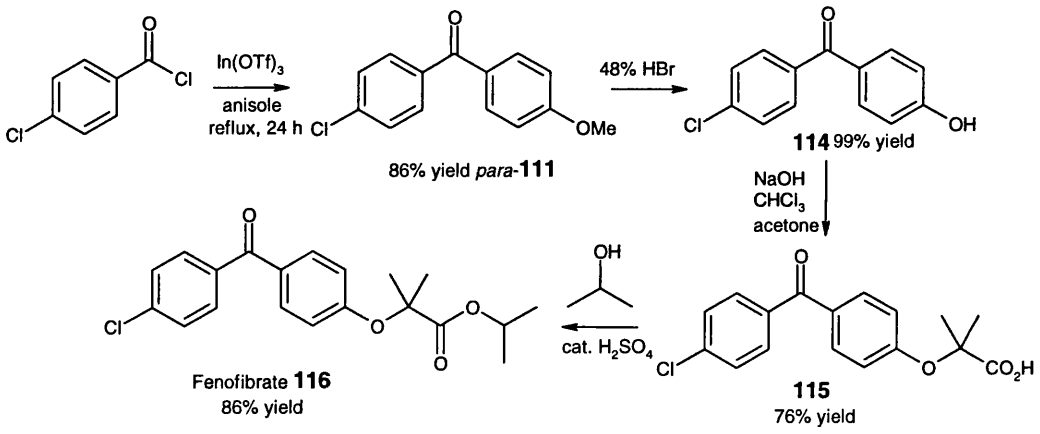
Entry	MX_3	R	R'	R''	Product & Yield(%)
1	$In(OTf)_3$	Me	H	Cl	**110**, 95[a]
2	$In(NTf_2)_3$	Me	H	Cl	**110**, 99[a]
3	$In(OTf)_3$	OMe	Cl	Cl	**111**, 99[b]
4	$In(OTf)_3$	H	H	Cl	**112**, 79
5	$In(NTf_2)_3$	H	H	Cl	**112**, 20
6	$In(OTf)_3$	H	H	OCOPh	**112**, 8.5
7	$In(OTf)_3$	Cl	H	Cl	**113**, 61[c]
8	$In(NTf_2)_3$	Cl	H	Cl	**113**, 5[c]
9	$Sc(OTf)_3$	H	H	Cl	**112**, 0
10	$Bi(OTf)_3$	H	H	Cl	**112**, 57[d]
11	$Ga(OTf)_3$	H	H	Cl	**112**, 85[e]

[a] *para:ortho* 88:12
[b] *para:ortho* 92:8.
[c] *para:ortho* 9:1.
[d] Ref.[108]
[e] Ref.[93]

The benzoylation of arenes was found to be less regioselective than the corresponding acylation, with around 10% of the minor *ortho* isomer formed. The isomeric ratio of ketones can be measured using ^1H NMR for example, for **110** the relative intensities of the ArCH_3 peak (*p*-**110** at δ2.36, *o*-**110** at δ2.52).

The synthetic utility of this process was shown in the synthesis of Fenofibrate, an anti-hyperlipemic. The first step was $In(OTf)_3$ catalysed benzoylation of anisole with 4-chlorobenzoyl chloride. Recrystallisation from anisole/light petroleum gave 86% yield of *para* **111**.

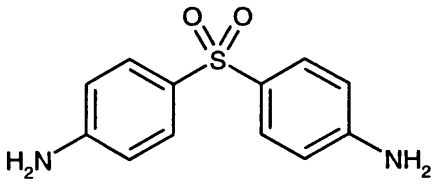
Demethylation to the phenol **114** was achieved using HBr in acetic acid. Compound **114** was characterised by the appearance of a broad singlet at δ6.15 in the ^1H NMR, representing the phenolic proton, together with the disappearance of the characteristic methoxy singlet at δ3.89 in the ^1H NMR and δ55.92 in the ^{13}C NMR. Fenofibric acid **115**, was formed on reaction with acetone and chloroform, resulting in the disappearance of the phenolic OH singlet at δ6.15 and the presence of a singlet at δ1.72 indicated the gem-dimethyl group. Sulfuric acid catalysed esterification with isopropyl alcohol gave Fenofibrate in good yield. The product **116** displayed doublet at δ1.21 and a multiplet at δ5.10 characteristic of an isopropyl group, and a mass spectrum M^+ of 360.8 consistent with the product.



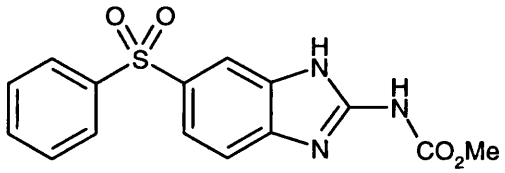
Scheme 64

2.3 Sulfonylation

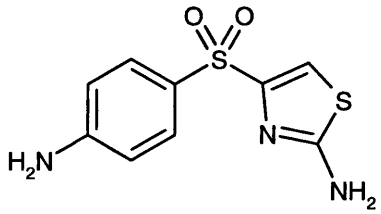
Organosulfones are versatile synthons in organic synthesis.[109] Diarylsulfones, such as Dapsone, Fenbendazole sulfone, Thiazolsulfone and Sulfetrone (Scheme 65) are important drugs for the treatment of such conditions as malaria, leishmaniasis, infections in patients with AIDS and discoid lupus erythematosus.[110] There exists a number of approaches to the synthesis of sulfones, including the oxidation of sulfoxides,[111] the reaction of sulfonyl halides[112] and aryl trifluoromethylsulfones[113] with organometallics and the Friedel-Crafts sulfonylation reaction.[114]



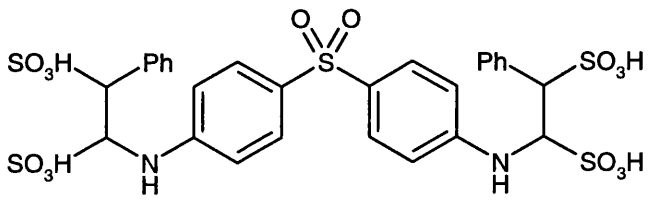
Dapsone



Fenbendazole sulfone



Thiazolsulfone



Sulfetrone

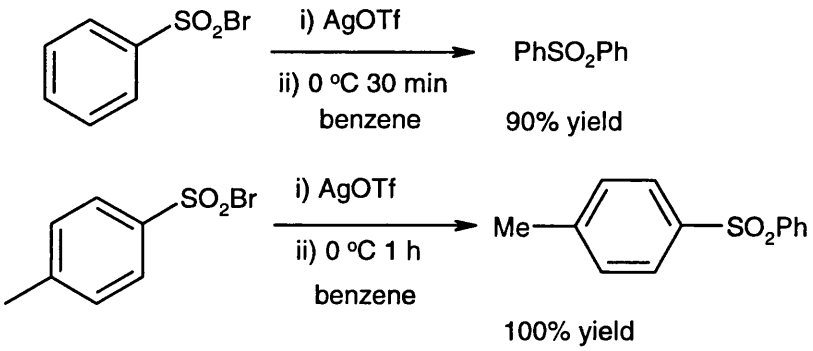
Scheme 65

Promotion of the Friedel-Crafts sulfonylation reaction is, like the Friedel-Crafts acylation reaction, a product-inhibiting reaction owing to the complexation of the Lewis acid with the produced sulfone.[114] Traditionally, the use of strong Lewis acids

such aluminium trichloride are employed in excess. Hence, the same environmental concerns are present as for the Friedel-Crafts acylation.

In contrast with the Friedel-Crafts acylation reaction, Brønsted acids are poor activators in the reaction of sulfonyl halides,[115] but are more effective for methane sulfonic anhydride.[116] Zeolites, clays[117] and Nafion-H[118] have been shown to be effective catalysts for Friedel-Crafts reactions of sulfonyl halides, sulfonic anhydrides and even sulfonic acids, although yields for the latter were only good for xylenes.

Effenberger *et a.* carried out the synthesis of aryl sulfones from sulfonyl bromides using stoichiometric silver triflate (Scheme 66).[115,119] The intermediate mixed sulfonic anhydride RSO_2OTf is highly electrophilic and reacts with arenes without a catalyst.[119]

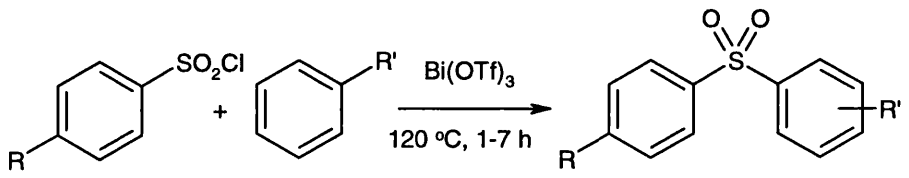


Scheme 66

Dubac and co-workers reported the use of bismuth(III) chloride and triflate in the sulfonylation of arenes in a sub-stoichiometric process.[108,120] Sulfonyl chlorides and sulfonic anhydrides react readily with activated and non- or weakly activated aromatics. $Bi(OTf)_3$ was described as having two behaviour patterns depending on the

sulfonylating agent. With sulfonyl chlorides (RSO_2Cl and $ArSO_2Cl$), the proposed mechanism involves ligand exchange (Cl^-/OTf^-) to generate electrophile ($ArSO_2OTf$ or RSO_2OTf) *in situ*. With sulfonic anhydrides, activation by $Bi(OTf)_3$ involves coordination to the sulfonyl groups enhancing the electrophilic activity. Exchange reactions are not possible with such substrates and yields are subsequently lower.

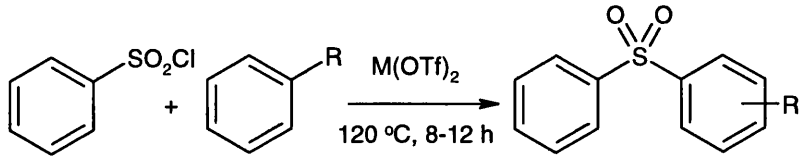
Triflic acid-doped bismuth(III) halides show similarly high catalytic activity in sulfonylation.[121]



Mol% $Bi(OTf)_3$	R	R'	Yield (%) (o:m:p)
5	H	OMe	80 (48:0:52)
5	Me	Me	80 (29:5:66)
10	H	Cl	70 (3:0:97)

Scheme 67

During the course of our studies, Singh and co-workers reported the use of both copper(II) and tin(II) triflate in sulfonylation reactions.[84] Whilst $Sn(OTf)_2$ was effective for a range of aromatics, $Cu(OTf)_2$ catalysed sulfonylations were limited to activated aromatics (Scheme 68).



Catalyst (mol%)	R	Yield (%) (*o:m:p*)
$Sn(OTf)_2$ (5)	Me	98 (37:4:59)
$Cu(OTf)_2$ (10)	Me	71 (36:4:60)
$Sn(OTf)_2$ (5)	Br	66 (5:0:95)
$Cu(OTf)_2$ (10)	Br	10 (4:0:96)

Scheme 68

2.3.1 Indium(III) Catalysed Sulfonylation

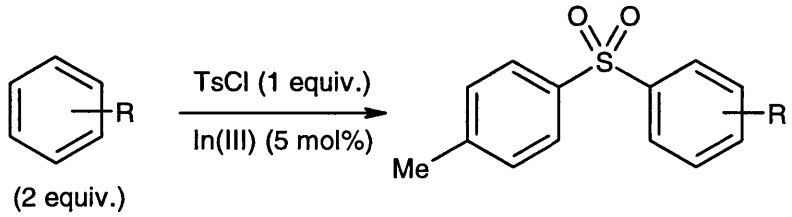
At the outset of the study we tested the efficacy of a selection of indium complexes in the sulfonylation of anisole and toluene with tosyl chloride. In a typical experiment, a mixture of aromatic (2 equiv.), tosyl chloride (1 equiv.) and indium(III) catalyst (5 mol%) were heated to 120 °C for typically 1-3 hours (Table 2.8). Reactions were monitored by TLC and on consumption of tosyl chloride the reaction mixture was cooled to ambient temperature and partitioned between water and dichloromethane. Purification by column chromatography gave the diarylsulfone **117** with an approximate 2:1 *para*:*ortho* regioselectivity. The product **117** is identified by the two ArCH_3 singlets at δ2.38 and δ2.41 and the two ArOCH_3 singlets at δ3.83 and δ3.85 with a high resolution mass spectrum of M^+ 263.07524.

Indium triflate and triflamide were found to be the most potent catalysts, affording the diaryl sulfone products in high yield (entries 1 and 7) although indium chloride and perchlorate were also effective catalysts (entries 5, 6 and 8).

$In(OTf)_3$ in combination with lithium perchlorate proved effective for sulfonylating anisole but it appears the lithium perchlorate has a detrimental effect when toluene is employed as the aromatic substrate (entries 1-2, 7 and 9). With 10 mol% lithium perchlorate (entry 3) or in the absence of catalyst no product was observed even with prolonged heating.

The lowering of temperature was detrimental to efficiency, the $In(OTf)_3$ catalysed sulfonylation of anisole with tosyl chloride giving 24% yield after 72 hours at room temperature.

Table 2.8 Sulfonylation with Tosyl Chloride and Indium(III) Complexes[a]



Entry	Catalyst	Temp. (°C)	Reaction Time (h)	Conversion % (Yield, %),	Isomer ratio[c]
1	$In(OTf)_3$	120	1	99(88)	38:0:62
2	$In(OTf)_3$ + 10 % $LiClO_4$	120	1.5	99	40:0:60
3	10 % $LiClO_4$	120	24	0	-
4	$In(acac)_3$	120	3	0	-
5	$In(ClO_4)_3$	120	1	85 (79)	33:0:67
6	$InCl_3$	120	1	65 (57)	40:0:60
7	$In(OTf)_3$[b]	120	1	99 (80)	38:0:62
8	$In(NTf_2)_3$[b]	120	3	99 (83)	38:0:62
9	$In(OTf)_3$ + 10 % $LiClO_4$[b]	120	2	50	45:0:55

[a] Reaction conditions: Tosyl Chloride (1 eq), Anisole/Toluene (2 eq). Catalyst 5 % In(III) complex.
[b] Toluene as aromatic substrate.
[c] (2,4': 3,4': 4,4').

The $In(OTf)_3$ catalysed sulfonylation was further investigated using a range of activated aromatics with sulfonyl chlorides and sulfonic anhydrides (Table 2.9). Aryl sulfonyl chlorides are the best sulfonylating agents (entries 1-10) giving high yields of diaryl sulfones in short reaction times. Alkyl sulfonyl halides and sulfonic anhydrides required longer reaction times and higher catalyst loading, but gave the desired sulfone in high yield. Tosic anhydride gave no reaction (entries 11 and 12).

Table 2.9 Sulfonylation of Activated Arenes

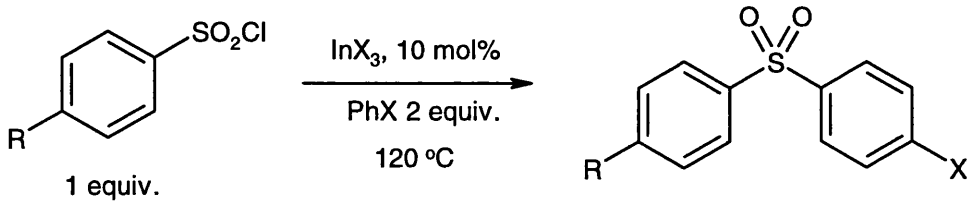
Entry	Sulfonylating agent	Arene[g]	Product and Yield (%)	Isomer ratio[d]
1	Tosyl chloride	A	**117** (80)	38:0:62[f]
2		B	**118** (88)	38:0:62[f]
3		B[a]	**118** (57)	40:0:60[f]
4		B[b]	**118** (79)	33:0:67[f]
5		C	**119** (78)	-
6		D	**120** (88)	-
7	Benzenesulfonyl chloride	A	**121** (92)	37:0:63[e]
8		B	**122** (98)	40:0:60[e]
9		C	**123** (96)	-
10	4-Bromobenzenesulfonyl chloride	A	**124** (78)	40:0:60[f]
11	Tosic anhydride	A	0	-
12		A[c]	0	-
13	Methanesulfonyl chloride	A	**125** (83)	52:19:29[e]
14	Methanesulfonic anhydride	A	**125** (73)	40:12:48[e]
15	*n*-Butanesulfonyl chloride	A	**126** (97)	50:15:35[e]

Reaction conditions: 120 °C; Arene/Sulfonylating agent 2/1; Catalyst 5 % (entries 1-12) or 10 % (entries 13-15); 2 hrs (entries 1-10) or 8 hrs (11-15).
[a] $InCl_3$ catalyst.
[b] $In(ClO_4)_3$ catalyst.
[c] Nitromethane as solvent.
[d] Calculated from ^1H NMR.
[e] (*o*:*m*:*p*).
[f] (2,4': 3,4': 4,4').
[g] Toluene (A), Anisole (B), Mesitylene (C), *m*-Xylene (D).

The sulfonylation of unactivated or deactivated aromatics, namely halobenzenes, was studied using $In(OTf)_3$. Reflecting the more demanding nature of the substrates (σ_p^+ = -0.071 to + 0.148), higher catalyst loading (10 mol%), a greater excess of aromatic substrate (5 equivalents ArH) and longer reaction times were employed.

The sulfonylation of halobenzenes with arylsulfonyl chlorides proceeded smoothly and with exclusive *para* selectivity under the influence of $In(OTf)_3$. Trifluorotoluene (BTF) ($\sigma_p^+ \approx +0.4$) was unaffected by the reaction conditions (entry 6). Indium trichloride and perchlorate were less effective than indium triflate (entries 2 and 3). An analogous inefficiency to that observed in the Friedel-Crafts benzoylation is observed in the indium triflamide catalysed sulfonylation.

Table 2.10 Sulfonylation of Deactivated Arenes



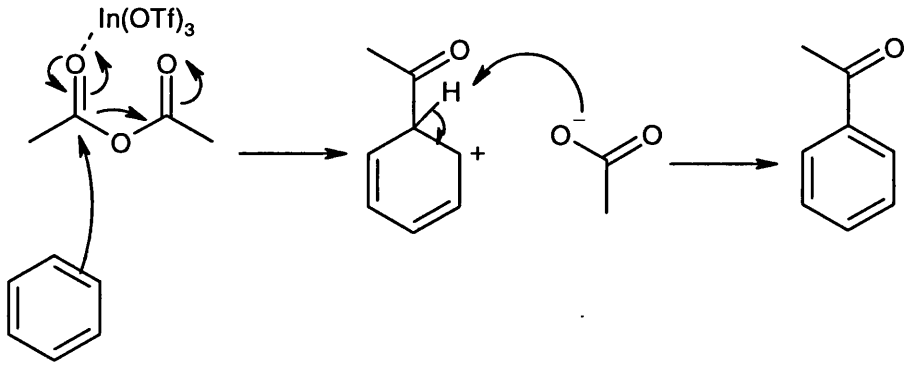
Entry	Sulfonylating agent	Arene[d]	Product and Yield
1	Tosyl Chloride	A	**127** (74)
2		A[a]	**127** (56)
3		A[b]	**127** (0)
4		B	**128** (71)
5		C	**129** (66)
6		D	0
7	Benzenesulfonyl chloride	A	**130** (84)
8		A[c]	**130** (0)
9	4-Bromobenzenesulfonyl chloride	A	**131** (54)

Reaction conditions: 120 °C; Arene/Sulfonylating agent 5/1; Catalyst 10 %; 18 hrs.
[a] $InCl_3$ catalyst.
[b] $In(ClO_4)_3$ catalyst.
[c] $In(NTf_2)_3$ catalyst
[d] Chlorobenzene (A), Bromobenzene (B), Fluorobenzene (C), Trifluorotoluene (D).

Indium triflate is an exceptional catalyst for the sulfonylation of activated and deactivated aromatics, forming the corresponding diaryl and alkyl aryl sulfones in high yield. The use of indium triflamide is limited to activated aromatics.

2.4 Mechanistic Aspects

A proposed mechanism for the activation of acetic anhydride by indium(III) salts alone is shown in Scheme 69. Co-ordination of a lone pair of electrons from the acetic anhydride to the Lewis acidic indium provides enhanced electrophilicity at the carbonyl carbon, resulting in attack from the aromatic nucleus. The acetate anion abstracts a proton, which results in aromatisation to give the product ketone. The more Lewis acidic indium(III) triflamide co-ordinates more strongly with the acetic anhydride which, in turn, results in faster reaction rates.

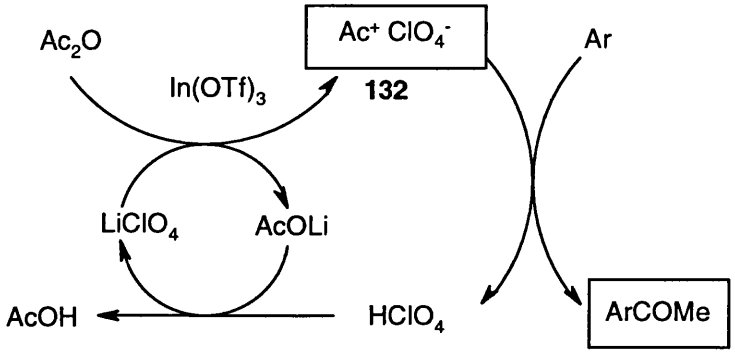


Scheme 69

The mechanism for the $In(OTf)_3$-$LiClO_4$ catalysed acylation reaction is believed to proceed via an intermediate formed from lithium perchlorate and acetic anhydride in the presence of indium triflate. In fact, if a homogeneous solution of $In(OTf)_3$ and $LiClO_4$ in diethyl ether is treated with acetic anhydride, a white precipitate is observed.

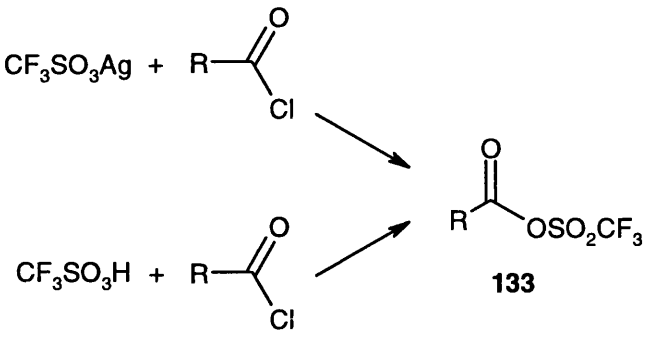
The absorption of the carbonyl groups in acetic anhydride in nitromethane was measured at 1826 and 1753 cm^{-1}. On addition of one equivalent lithium perchlorate and 5 mol% indium triflate, the absorption is measured at 1807 and 1715 cm^{-1}.

A postulated mechanism is shown in Scheme 70. The cationic intermediate **132** generated from $LiClO_4$ and Ac_2O in the presence of $In(OTf)_3$. Reaction with an arene gives the desired aromatic and perchloric acid, which reacts with lithium acetate to regenerate the lithium perchlorate.



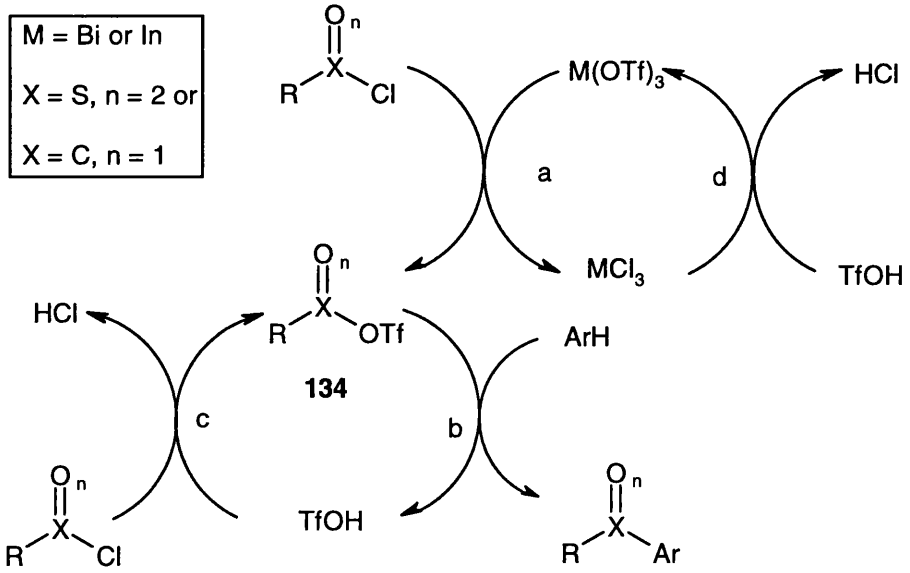
Scheme 70

Silver triflate has been shown to promote Friedel-Crafts acylation reactions with acid chlorides in a stoichiometric process, generating a carboxylic triflic anhydride **133**, whose strong electrophilic nature allows acylations reactions to proceed without a catalyst.[122] Effenberger also showed that **133** could be formed through the reaction of triflic acid with acid chlorides,[82] and that acylation reactions are catalysed efficiently by as little as 1 mol% triflic acid. Perchloric acid, having about the same acid strength, is a considerably less effective catalyst, suggesting acyl triflates are formed in the triflic acid catalysed process. The generation of mixed sulfonic anhydrides $RSO_2OSO_2CF_3$ from sulfonyl halides and silver triflate allows the sulfonylation of arenes in high yield.[107,111]



Scheme 71

Bismuth triflate catalysed benzoylation[92,108] and sulfonylation[108,120] of arenes proceeds via exchange of triflate and chloride anions, generating benzoyl or sulfonyl triflate **134** and bismuth chloride (Scheme 72, step a). On reaction with an arene, triflic acid is regenerated (Scheme 72, step b). For benzoylation reactions triflic acid is the true catalyst of the reaction (Scheme 72, steps b, c).



Scheme 72

Metal triflates that cannot undergo such an exchange process, such as the triflates of copper, tin, scandium and other rare earth metals, and are subsequently inefficient catalysts for the reaction of benzoyl chloride with toluene, benzene or halobenzenes.

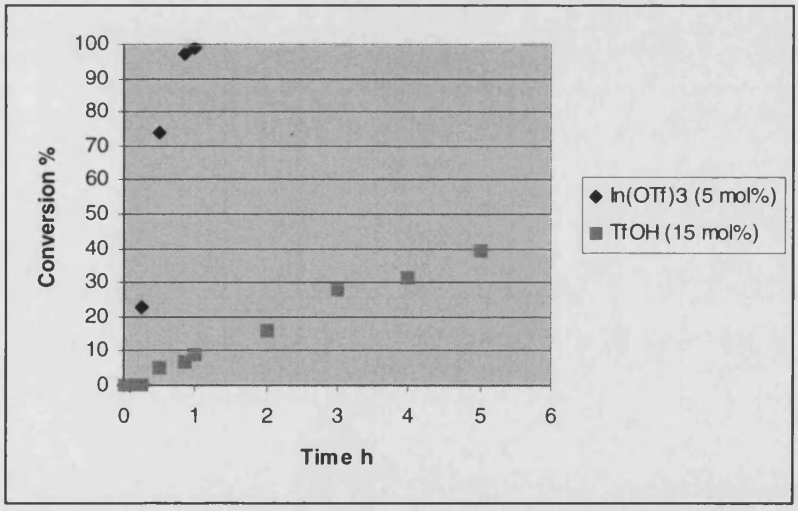
Experimental observations led us to assume that an analogous exchange process was occurring in the indium triflate catalysed benzoylation and sulfonylation reactions. Firstly, the exceptional efficiency of $In(OTf)_3$ with PhCOCl or $ArSO_2Cl$ for the benzoylation and sulfonylation of benzene and its halogenated derivatives. Secondly, $In(OTf)_3$ catalysed benzoylation and sulfonylation of unactivated aromatics proceeds very slowly or not at all when benzoic or tosic anhydrides are used. Such substrates would exclude any ligand exchange, and catalysis can occur only by co-ordination.

In order to investigate if such an exchange process was indeed occurring, we undertook spectroscopic experiments in order to detect the benzoyl triflate intermediate.

Benzoyl triflate was prepared by treating silver triflate with an equimolar amount of benzoyl chloride in deuterated benzene. A shift in the ^{19}F NMR signal from δ-72.54 ($AgOSO_2CF_3$) to δ-73.27 representing the formation of benzoyl triflate ($PhCOOSO_2CF_3$) as detailed by Effenberger.[122] When indium triflate was treated with a three-fold excess of benzoyl chloride an analogous signal was observed. The singlet peak δ-17.52, representing indium triflate diminishes, and a new singlet at δ-73.45 was observed. This data suggests that triflate/chloride exchange can occur at indium(III).

It is uncertain whether the $In(OTf)_3$ catalysed benzoylation proceeds via a metal mediated pathway (Scheme 72, steps a, b, d) or, like $Bi(OTf)_3$, a proton mediated pathway (Scheme 72, steps b, c). However, $In(OTf)_3$ (5 mol%) catalysed benzoylation occurs at a slower rate to the triflic acid (15 mol%) catalysed reaction,[108] suggesting the proton mediated pathway is not favoured.

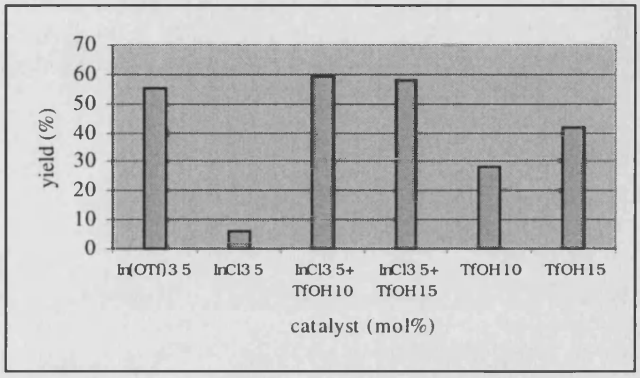
In order to see whether triflic acid itself was the catalyst for sulfonylation reactions (rather than $In(OTf)_3$) a reaction rate investigation was carried out. The catalytic activity of 5 mol% $In(OTf)_3$ and 15 mol% triflic acid in the sulfonylation of toluene with benzenesulfonyl chloride was compared (Scheme 73).



Scheme 73

As Scheme 73 shows, 5 mol% $In(OTf)_3$ is much more efficient than 15 mol% triflic acid, suggesting that an indium-mediated process (Scheme 72, steps a, b, d) is occurring and that triflic acid *alone* is not the actual catalyst of the reaction.

By using 5 mol% $InCl_3$ in combination with 10 or 15 mol% triflic acid, the same conversions are achieved as when 5 mol% $In(OTf)_3$ is employed in the sulfonylation of chlorobenzene with benzenesulfonyl chloride, whilst both triflic acid and 5 mol% $InCl_3$ alone are poor catalysts for this reaction. This suggests that a mixed ligand complex, $InCl(OTf)_2$ may be the true catalyst for sulfonylation reactions.



Scheme 74

Ligand exchange is believed to be possible because of the similar energies of the metal-oxygen and metal-chlorine bonds. For bismuth (337 and 301 kJ mol^{-1} respectively) and indium (320 and 439 kJ mol^{-1} respectively) the strengths are similar, allowing exchange to occur. However, if the metal-oxygen bond energy is much stronger than the metal-chlorine one (Sc 681 and 383 kJ mol^{-1}) exchange reaction cannot take place and the metal triflate will be a poor catalyst for sulfonylation.

The bond energies for Sn-O (531 kJ mol^{-1}) and Sn-Cl (414 kJ mol^{-1}), and Ga-O (481 kJ mol^{-1}) and Ga-Cl (353 kJ mol^{-1}) suggest ligand exchange at these metals is possible, and the high catalytic activity of the triflates of tin[84] and gallium[99] in

sulfonylation reactions has been reported. Bond energy data suggests that the triflates of Pb and Sb may also be efficient catalysts.

The inefficiency of $In(NTf_2)_3$ in both sulfonylation and benzoylation reactions may be due to the low nucleophilicity of the triflamide anion, and subsequent inability to form the analogous benzoyl triflamide ($PhCONTf_2$). In $(CF_3SO_2)_2N^-$, electron delocalisation is extensive from sp^2-hybridised nitrogen into 3d orbitals of sulfur.[123]

In conclusion, this chapter demonstrates the use of indium(III) complexes in electrophilic aromatic substitution reactions. Indium triflate has been shown to be highly catalytic in the acylation (in combination with lithium perchlorate) at low catalyst loadings ($\geq$ 1 mol%). The ability of indium triflate to undergo ligand exchange means it is a highly efficient catalyst for benzoylation and sulfonylation reactions, allowing the functionalisation of activated and deactivated aromatics.

The enhanced Lewis acidity imparted by the more weakly co-ordinating counterions in $In(NTf_2)_3$, result in higher catalytic activity in acylation reactions. However, the inherent low nucleophilicity of these counterions precludes the highly efficient ligand exchange process that occurs with $In(OTf)_3$. Subsequently, yields for the benzoylation and sulfonylation of deactivated aromatics are poor.

During the course of our studies, Dubac and Le Roux published a review of the use of $Bi(OTf)_3$ in Friedel-Crafts reactions.[108] A comparison of metal triflates as catalysts for benzoylation and sulfonylation reactions revealed bismuth, gallium, indium and silver triflates to be the most efficient.

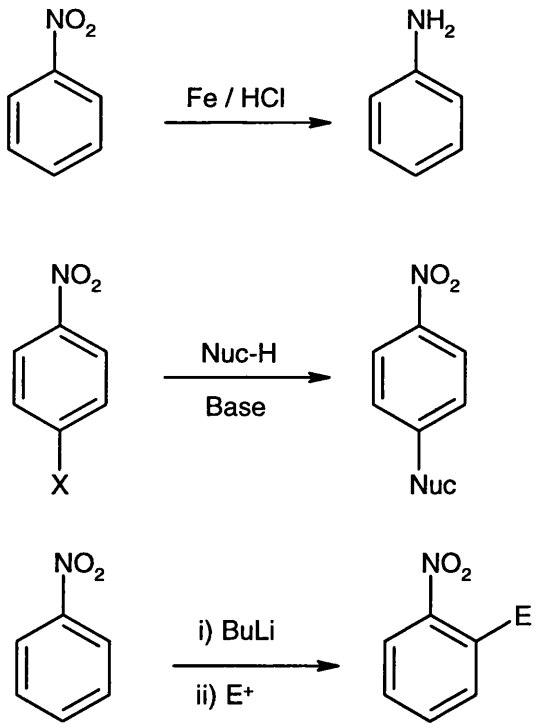
CHAPTER 3

AROMATIC NITRATION

3 Aromatic Nitration

3.1 Introduction

The nitration of aromatics is a common reaction in the preparation of bulk and fine chemicals.[124] Nitroaromatics are widely used in the synthesis of dyes, pharmaceuticals, perfumes and plastics. They are also useful intermediates, for example in the synthesis of aniline derivatives, and are good substrates for nucleophilic aromatic substitution and *ortho* lithiation (Scheme 77).



Scheme 77

Although dilute nitric acid is effective for nitrating reactive substances such as phenol, nitrations typically require the use of potent mixtures of fuming nitric and sulfuric acid. Sulfuric acid is the catalyst for the formation of the nitronium ion **135**, recognised as the nitrating agent.[124]

$$HNO_3 + H^+ \rightleftharpoons NO_2^+ + H_2O$$

135

Alternatives to sulfuric acid such as perchloric,[125] trifluoroacetic,[126] methanesulfonic[127] and trifluoromethanesulfonic[128] acid have also been reported. The by-product of the nitration reaction using nitric acid, water, slows the reaction by diluting the acid, and, as such, a large excess of acid is required. This leads to excessive acid waste streams and added expense.

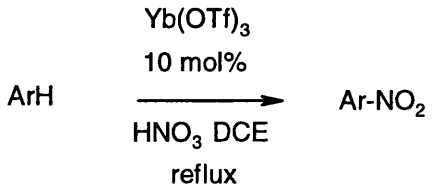
In an effort to reduce the amount of acidic waste, a number of methods using solid acid catalysts have been reported. These include the use of nitrates of transition metals on K10 montmorillonite,[129] nitric acid or alkyl nitrates over Nafion-H[130] and sulfuric acid on silica gel.[131]

Nitric acid may also be used in conjunction with Lewis acids.[132] However, Lewis acids such as BF_3 are used in stoichiometric quantities and are destroyed on aqueous work-up.

Barrett and co-workers reported the use of lanthanide(III) triflates as catalysts for the nitration of aromatics in an atom efficient process, using 69% nitric acid, where water is the only by-product.[133] Sub-stoichiometric (10 mol%) $Yb(OTf)_3$ was found to be

the most effective of the lanthanides, catalysing the nitration of simple aromatics, such as alkyl bearing aromatics, naphthalene and bromobenzene in high yield. Ytterbium triflate was recovered from the reaction mixture and could be re-used without adverse effects on either the rate or yield of the reaction.

Table 3.1 Ytterbium triflate catalysed nitration

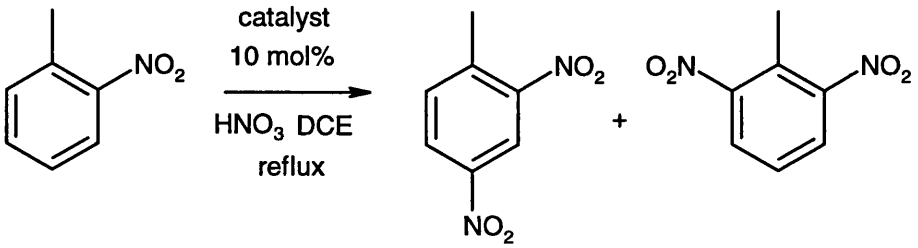


ArH	Conversion (%)
Benzene	>95
Biphenyl	89
p-Xylene	>95

An inverse correlation between ionic radii of the lanthanide ions and the extent of reaction was observed. Effectively, the higher the charge-to-size ratio, the more effective the nitration catalyst. With this in mind, the triflates of two tetrapositive metal centres, hafnium (r^{4+} = 0.78 Å, z/*r* = 5.13) and zirconium (r^{4+} = 0.79 Å, z/*r* = 5.06), were screened for catalytic activity in nitration reactions.

Both catalysts were found to be highly effective for the nitration of *o*-nitrotoluene **136** to dinitrotoluene **137** (σ_p^+ = + 0.7) for which ytterbium triflate is poorly active (Table 3.2).[134]

Table 3.2 Hafnium and Zirconium catalysed nitration



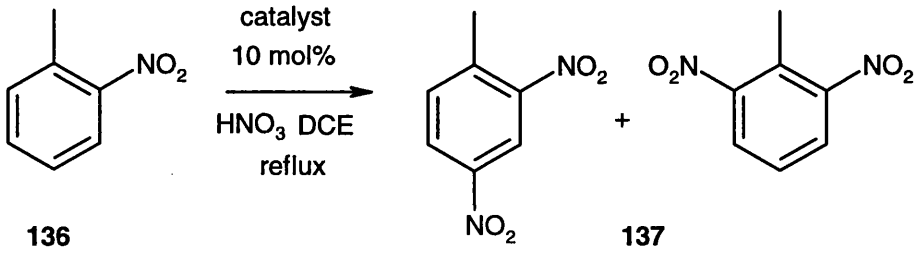
136 **137**

Catalyst	Time (h)	Conversion (%)
$Yb(OTf)_3$	120	17
$Hf(OTf)_4$	24	>95
$Zr(OTf)_4$	24	>95

The mechanism is believed to involve binding of a nitrate ion to the metal centre, liberating a proton, which generates NO_2^+ from nitric acid in the classic manner. The nitronium ion is then transported to the organic phase, solubilised by the triflate counterion.

A more weakly co-ordinating anion $^-C(SO_2CF_3)_3$ was employed in order to increase the acidity of the metal centre and increase the solubility of the $NO_2^+X^-$ ion pair. Ytterbium and scandium tris(trifluoromethylsulfonyl)methides, $Yb(CTf_3)_3$ and $Sc(CTf_3)_3$ were found to be highly effective catalysts for nitration reactions.[135]

Table 3.3 Lanthanide(III) triflate and methide catalysed nitrations



136 **137**

Catalyst	Conversion (%)
$Yb(OTf)_3$	8
$Sc(OTf)_3$	50
$Yb(CTf_3)_3$	93
$Sc(CTf_3)_3$	91

Indium(III) salts are well documented as behaving as strong Lewis acids in aqueous media (Chapter 1), and possess a relatively high charge-to-size ratio of 3.75 (r^{3+} = 0.80 Å). We supposed that indium salts would be effective catalysts for the nitration of aromatics.

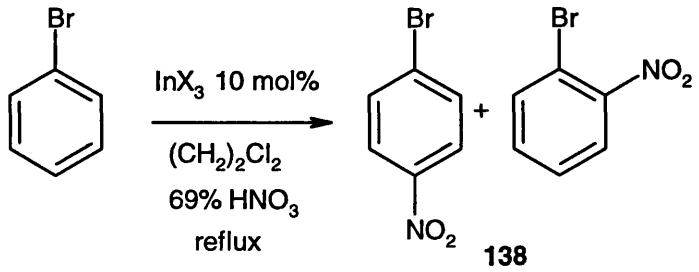
3.2 Indium Triflate in Aromatic Nitration

Initial studies showed that, indeed, indium(III) salts are effective catalysts for aromatic nitration. Bromobenzene in dichloroethane was treated with 10 mol% indium triflate and one equivalent of 69% nitric acid, and the resultant mixture was heated to reflux for 6 hours. The reaction mixture exists as a biphasic mixture, with the denser aqueous phase containing the indium catalyst and nitric acid, and the organic phase containing the aromatic substrate and product. Over the course of the reaction, the aqueous phase diminishes until there is no apparent phase boundary.

On cooling to room temperature, the organic phase was washed with water, dried and concentrated. Crude ^{1}H NMR showed that bromobenzene had been nitrated to bromonitrobenzene **138** in 50% conversion in 6 hours and with a 2:1 *para:ortho* ratio. The two regioisomers were easily separated by column chromatography (hexane:ethyl acetate 9:1).

Extension of the reaction time to 18 hours resulted in high yield of the nitrated products. The use of indium trichloride gave no product (Table 3.4).

Table 3.4 Indium(III) catalysed nitration of bromobenzene



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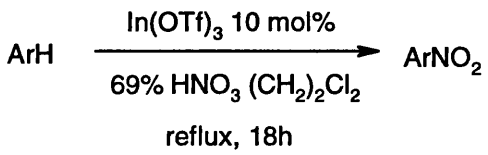
Catalyst	Time (h)	Conversion (%) (o:p)
$InCl_3$	6	0
$In(OTf)_3$	6	50 (34:66)
$In(OTf)_3$	18	89 (44:56)

Using the developed conditions (10 mol% $In(OTf)_3$, 1 equivalent 69% HNO_3, dichloroethane, reflux, 18 h), a number of more electron-rich aromatics were also successfully nitrated, giving the corresponding mono nitro compounds in high yield. However, the nitration of anisole (σ_p^+ = -0.76) under these conditions resulted in a complex mixture of mono and dinitro derivatives as well as tar-like material. More electron-deficient aromatics (nitrobenzene σ_p^+ = +0.78, 2-nitrotoluene $\sigma_p^+ \approx +0.7$) were unaffected by the reaction conditions. In all cases the isomer distribution obtained from the nitrations were consistent with direct attack by a nitronium ion.

Table 3.5 Nitration of aromatics with $In(OTf)_3$

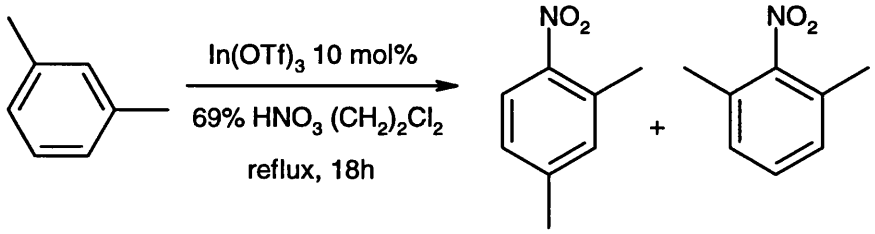


Entry	ArH	Yield (%)	Product and Isomer ratio
1	Toluene	99	**139**, 50:6.5:43.5[a]
2	*m*-Xylene	99	**140**, 86:14[b]
3	Naphthalene	99	**141**, 91:9[c]
4	2-Nitrotoluene	0	-
5	Nitrobenzene	0	-

[a] o:m:p.
[b] 4-NO_2:2-NO_2.
[c] 1-NO_2:2-NO_2.

The aqueous washings obtained on work-up, containing both the catalyst and nitric acid can be evaporated under reduced pressure to furnish the indium(III) salt as a white solid, which can be recycled and used repeatedly without loss of activity (Table 3.6).

Table 3.6 Recycling indium(III) triflate for the nitration of *m*-xylene



140

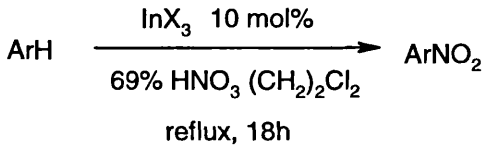
Run	Yield (%)
1	99[a]
2	98[a]
3	99[a]

[a] Isomer ratio: 86:14 (4-NO_2:2-NO_2).

3.3 Indium Triflamide in Aromatic Nitration

In the previous chapter, the use of indium(III) bis(trifluoromethylsulfonyl)amide in place of indium(III) triflate was found to impart enhanced catalytic activity in Friedel-Crafts acylations with acetic anhydride. We postulated that the increased acidity of the indium centre in $In(NTf_2)_3$ would also impart enhanced catalytic activity in the nitration of aromatics. We also hoped that the increased solubility of the $Tf_2N^- NO_2^+$ salt in organic solvents would facilitate more efficient nitration.

Table 3.7 Nitration of aromatics with $In(NTf_2)_3$



Entry	Aromatic	Yield (%)		Product and Isomer Ratio
		$In(OTf)_3$	$In(NTf_2)_3$	
1	Toluene	99	99	**139**, 48:7:45[a]
2	*m*-Xylene	99	99, 99, 99[b]	**140**, 14:86[c]
3	Bromobenzene	89	98	**138**, 39:0:61[a]
4	2-Nitrotoluene	0	31	**137**, 35:65[d]
5	Chlorobenzene		93	**142**, 33:0:67[a]
6	*o*-Toluic acid		99	**143**, 44:56[e]
7	*p*-Toluic acid		84	**144**

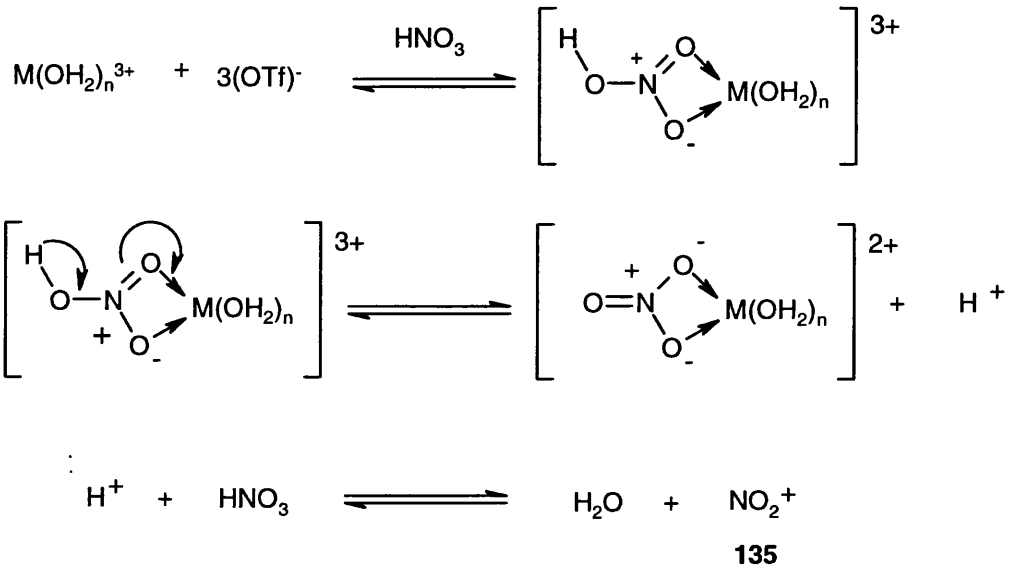
[a] *o*:*m*:*p*.
[b] Recycled catalyst runs,
[c] 2-NO_2:4-NO_2.
[d] 2,6-NO_2:2,4-NO_2.
[e] 3-NO_2:5-NO_2.

Indium triflamide was found to be a more efficient catalyst than indium triflate. Whilst both catalysts effected the nitration of electron-rich aromatics (entries 1,2), a discernible difference in efficacy occurred when nitrating more demanding substrates (entries 3,4). Other electron-deficient aromatics were nitrated in high yield using $In(NTf_2)_3$ (entries 5-7). It has also been shown that $In(NTf_2)_3$ can be recycled through the aqueous phase on work-up.

Nitration of *m*-xylene and bromobenzene can be achieved in the presence of just 1 mol% $In(NTf_2)_3$, however the reaction is slower (*m*-xylene: from 99% yield to 76% yield, bromobenzene: from 98% yield to 47% yield).

3.4 Mechanistic Considerations

The postulated mechanism for indium(III) catalysed nitration is shown in Scheme 78. The binding of a nitric acid molecule to the indium metal centre is followed by the generation of a proton, which in turn generates the nitronium ion **135**. **135** then diffuses into the organic phase accompanied by a triflate counterion.



Scheme 78

This mechanism is analogous to that of the lanthanide-mediated process[136] and rationalises the observed dependency of catalytic efficacy on the charge-to-size ratio. As the ionic radii of the metal decreases, this proton release becomes increasingly facile as the metal becomes more polarising.

Indium(III) has a charge-to-size ratio (3.75 z/*r*) between that of the lanthanides (2.56-3.00 z/*r*) and hafnium(IV) (5.13 z/*r*) and shows intermediate catalytic activity. The

$In(OTf)_3$ catalysed nitration of *m*-xylene proceeds in 95% conversion in 5 hours. Using $Yb(OTf)_3$, (2.98 z/*r*) the conversion is slightly lower (89%).[136] Whilst $Hf(OTf)_4$ catalyses the nitration of *o*-nitrotoluene in >95% conversion,[134] $In(OTf)_3$ is essentially ineffective.

The inherent acidity conferred on $In(NTf_2)_3$ by its more weakly co-ordinating triflamide counterion is believed to lead to faster rates. The increased solubility in organic solvents of the ion pair generated, $Tf_2N^- NO_2^+$,[137] may also contribute to the more efficient nitration observed.

In conclusion, indium triflate catalyses the nitration of aromatics with nitric acid. Activated and slightly deactivated aromatics are nitrated, with a lower reactivity limit of bromobenzene ($\sigma_p^+ = +0.15$). More deactivated aromatics are unaffected by the reaction conditions, thus indium triflate is not as efficient as hafnium(IV) and zirconium(IV) triflates.

The use of indium triflamide allows the nitration of a wider range of aromatics including benzoic acid derivatives and 2-nitrotoluene, albeit in moderate yield. Both catalysts can be recycled and reused through aqueous extraction of the reaction mixture.

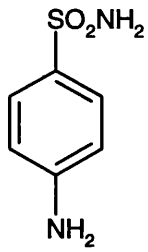
CHAPTER 4

SULFAMOYLATION

4 Sulfamoylation

4.1 Introduction

Aromatic sulfonamides are of significant interest to the synthetic chemist due to their bioactive nature, most notably as pharmaceuticals. Over 30 drugs containing this functionality are in clinical use including; antibacterials (such as sulphanilamide **145** and sulfadiazine **146**), diuretics (such as dorzolamide **147**), anticonvulsants (such as acetazolamide **148**), hypoglycemics, HIV protease inhibitors and vaso dilators.[138]



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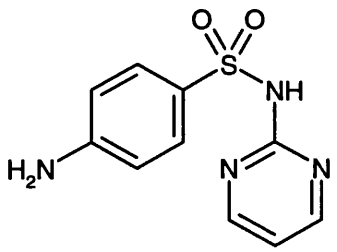
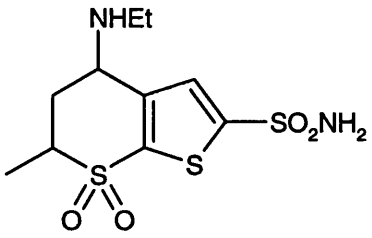
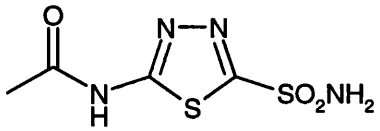


146



147

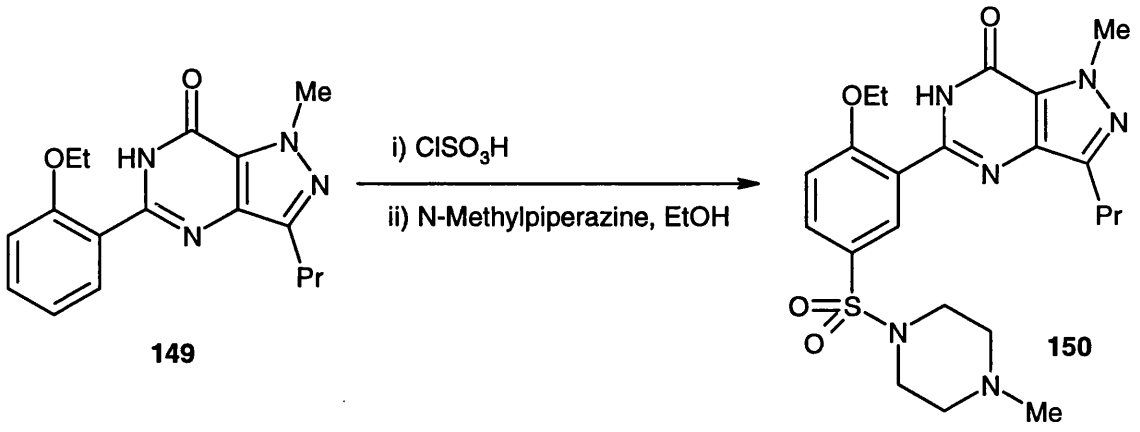


148

Scheme 79

The most popular route to aromatic sulfonamides involves the chlorosulfonation of an arene, to give the sulfonyl chloride, and subsequent reaction with an amine,[139] as demonstrated in the final step of the synthesis of Viagra **150**. Chlorosulfonylation of the phenyl ring of **149** allows coupling with *N*-methylpiperazine (Scheme 80). This approach, however is marred by either the need to employ a large excess of

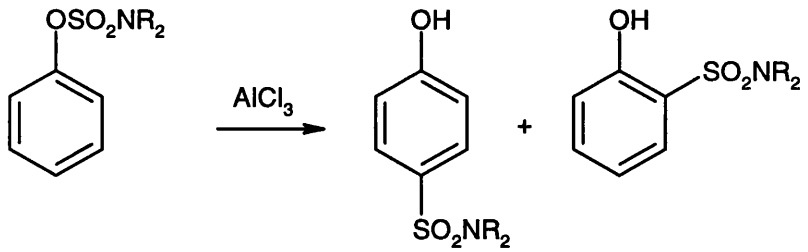
chlorosulfonic acid, which leads to acidic waste, or the undesirable formation of the diaryl sulfone.[140]



149 150

Scheme 80

Electrophilic substitution reactions introducing the SO_2NR_2 moiety directly have less precedent. An Irish group reported the aluminium trichloride promoted thia-Fries rearrangement of aryl *N,N*-dialkylsulfamates **151** to aryl sulfonamides **152** and **153** (Scheme 81).[141]

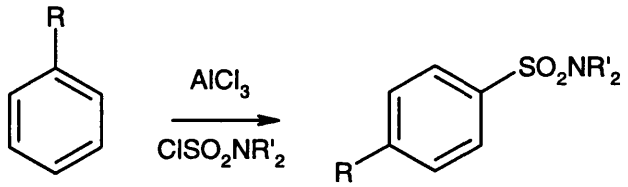


151 **152** **153**

R = Me, Et, *n*-Pr
67-88% yield

Scheme 81

Gupta reported the aluminium trichloride promoted formation of *N,N*-dialkylsulfonamides from the corresponding sulfamoyl chlorides (Scheme 82). A mixture of $AlCl_3$ and dialkylsulfamoyl chlorides **155** in an excess of aromatic substrate **154** was heated to reflux for 1-4 hr giving the arylsulfonamides **156** in moderate to high yield.[142]

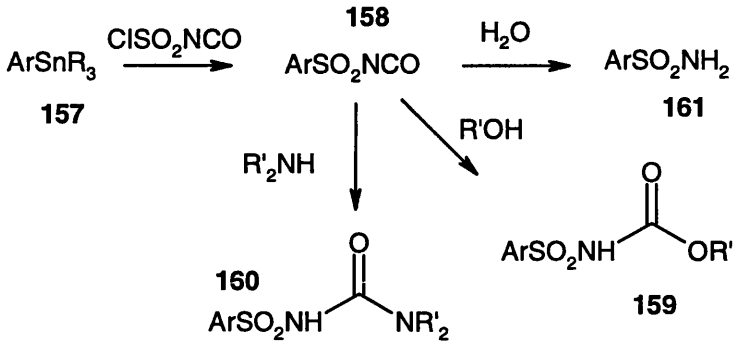


154 **155** **156**

R	NR'_2	Yield (%)
H	NEt_2	94
H	$N(CH_2)_5$	100
Me	NEt_2	90
Cl	NEt_2	60

Scheme 82

The reaction of chlorosulfonyl isocyanate with trialkylstannyl-substituted arenes **157** provides the aromatic sulfonyl isocyanates **158**.[143] The isocyanates can be trapped with an alcohol or amine to give arylsulfonylcarbamates **159** and arylsulfonylureas **160** respectively. Hydrolysis *in situ* gives the arylsulfonamide **161**.



Scheme 83

The use of stoichiometric Lewis acids or tin reagents is undesirable, due to the inherent acidic and toxic waste problems. We sought to employ indium(III) Lewis acids as catalysts for the formation of aryl sulfonamides in a one-step process from sulfamoyl chlorides.

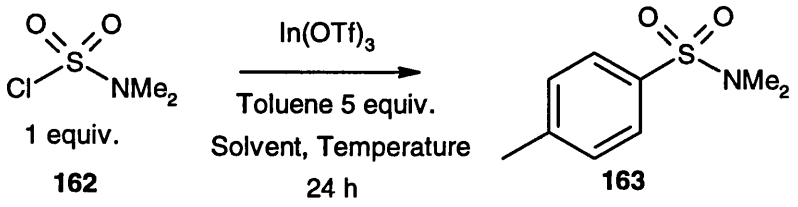
4.2 Catalytic Sulfamoylation

An initial study was undertaken in order to optimise conditions for an indium(III) catalysed sulfamoylation reaction (Table 4.1). Commercially available *N,N*-dimethylsulfamoyl chloride **162** and toluene were chosen for this investigation. The reactions were monitored by TLC (light petroleum : ethyl acetate, 4:1), with the consumption of *N,N*-dimethylsulfamoyl chloride (R_f = 0.4) coinciding with the formation of *N,N*-dimethyl-*p*-toluenesulfonamide **163** (R_f = 0.25). Spectroscopic analysis supported the formation of **163**. The introduction of the *N,N*-dimethyl group to the aryl ring was denoted in the ^{1}H NMR by the appearance of a singlet of intesity six at δ2.68 and the disappearance of the singlet at δ2.96 representing the *N,N*-dimethyl groups of *N,N*-dimethylsulfamoyl chloride. Compound **163** was confirmed by a high resolution mass spectrum of M^+ 199.0659.

The influence of solvent, temperature and catalyst loading are detailed in Table 4.1. Dichloroethane was shown to be the optimum solvent (entries 8 and 9), although solvent-free conditions (akin to the sulfonylation reaction) also resulted in moderate conversion (entries 3-5). The ideal reaction temperature appeared to be 100 °C, with lower (50 °C) and higher (120 °C) temperatures resulting in lower yields (entries 3-5).

It was observed that strictly anhydrous conditions were required (distilled solvents, flame-dried apparatus and molecular sieves). Without such conditions, Me_2NSO_2Cl decomposed rapidly, presumably to Me_2NSO_2OH in the presence of $In(OTf)_3$.

Table 4.1 Optimisation of $In(OTf)_3$-catalysed sulfamoylation



Entry	$In(OTf)_3$ (mol%)	Solvent	Yield (%)[a]
1	10	Nitromethane	34
2	10	Dimethylacetamide	0
3	10	Toluene	17[b]
4	10	Toluene	54
5	10	Toluene	41[c]
6	1	DCE	9
7	5	DCE	30
8	10	DCE	60
9	20	DCE	86
10	20	DCE	0[d]

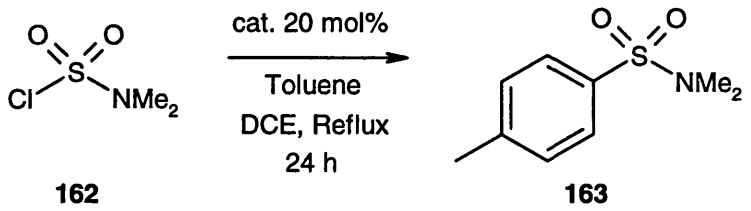
[a] Isolated yield.
[b] 50 °C.
[c] 120 °C.
[d] 1.2 equiv. **163** added.
Conditions: *N,N*-Dimethylsulfamoylchloride, 100 °C, 24 h, 5 equiv. Toluene.

By employing 20 mol% $In(OTf)_3$ a high yield of the desired sulfonamide was obtained (entry 9). For entries 8 and 9, the yield is 6 times the catalyst loading (60% for 10 mol% catalyst and 30% yield for 5 mol% catalyst); this suggests that six of the product sulfonamide molecules inhibit one of the catalyst. Indeed, addition of 1.2 equivalents of *N,N*-dimethyl-*p*-toluenesulfonamide to the reaction resulted in total inhibition of $In(OTf)_3$ catalysis (entry 10).

The use of lithium perchlorate, in combination with indium triflate, resulted in violent effervescence and blackening of the reaction mixture. Further reactions with lithium perchlorate were not attempted.

A screen of Lewis acid catalysts using these optimised conditions (20 mol% catalyst, 5 equiv. toluene, 1 equiv. **162**, DCE, 24 h, 100 °C) revealed $In(OTf)_3$ to be the best catalyst (Table 4.2, entry 2), although indium chloride and indium triflamide were moderately effective catalysts (entries 3 and 4).

Table 4.2 Effect of Lewis acid in sulfamolyation of toluene



162 **163**

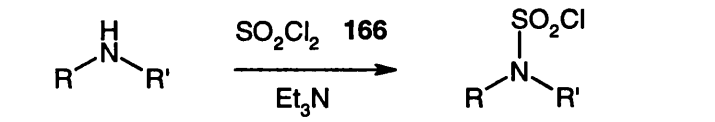
Entry	Catalyst	Yield (%)[a]
1	$AlCl_3$	20
2	$In(OTf)_3$	86
3	$InCl_3$	43
4	$In(NTf_2)_3$	35
5	$Sc(OTf)_3$	19
6	$La(OTf)_3$	0
7	$Yb(OTf)_3$	0
8	$Bi(OTf)_3$	19
9	AgOTf	15
10	TfOH	9

Conditions: Me_2NSO_2Cl, 20 mol%, 24 h, 5 equiv. Toluene, DCE, 100 °C.
[a] Isolated yield.

Other metal triflates (Bi, Sc, La and Yb), triflic acid and aluminium trichloride proved poorly active (entries 1, 5-8, 11). The moderate efficacy of silver triflate must be due to OTf^-/Cl^- exchange, generating Me_2NSO_2OTf *in situ*.

4.2.1 Indium Triflate in Sulfamoylation

In order to extend the methodology to allow the synthesis of a range of arylsulfonamides, two further sulfamoyl chlorides, *N,N*-diethyl- and 1-piperidylsulfamoyl chloride, were prepared. Using the method reported by Gupta (Scheme 85),[142] a mixture of triethylamine and the corresponding dialkyl amine **164** or **165** was added to a solution of sulfuryl chloride **166** in chloroform at 0 °C over an hour. Following aqueous work-up, the crude product is distilled to give the desired *N,N*-dialkylsulfamoyl chlorides **167** and **168** in moderate yield.



164 R = R' = Et
165 R = R' = -$(CH_2)_4$-

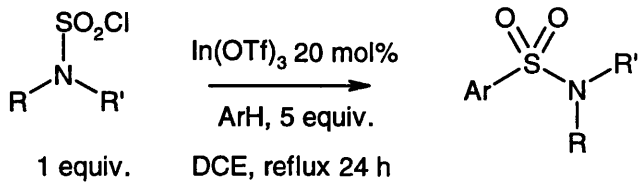
167 R = R' = Et
168 R = R' = -$(CH_2)_4$-

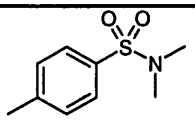
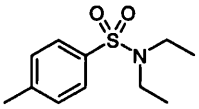
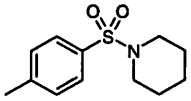
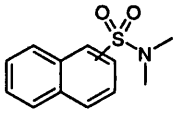
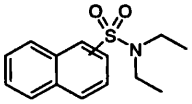
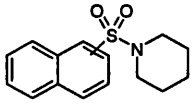
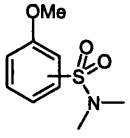
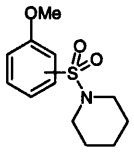
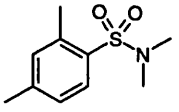
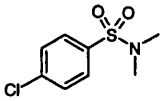
Scheme 85

Analysis of **167** showed the absence of an N-H signal and the presence of two signals, a triplet at δ1.30 and a quartet at δ3.42 in the ^{1}H NMR and two signals, at δ12.7 and δ45.0 in the ^{13}C NMR. Three multiplet signals were observed in the ^{1}H NMR spectrum of **168**, at δ1.55-1.65, δ1.72-1.84 and δ3.15-3.40. Boiling points for both products were consistent with those found in the literature.[142]

A number of arenes and sulfamoyl chlorides were subjected to the optimised conditions, 20 mol% $In(OTf)_3$, 5 equivalents of aromatic substrate and 1 equivalent of sulfamoyl chloride in refluxing DCE for 24 h (Table 4.3).

Table 4.3 Variation in substrates



Entry	Arene	Sulfamoyl Chloride	Product	Yield (%)
1	Toluene	Dimethyl	 **163**	86 (0:100)[a]
2		Diethyl	 **169**	64 (0:100)[a]
3		Piperidyl	 **170**	51 (0:100)[a]
4	Naphtalene	Dimethyl	 **171**	99 (34:66)[b]
5		Diethyl	 **172**	44 (37:63)[b]
6		Piperidyl	 **173**	56 (24:76)[b]
7	Anisole	Dimethyl	 **174**	99 (45:55)[a]
8		Piperidyl	 **175**	80[d] (36:64)[a]
9	*m*-Xylene	Dimethyl	 **176**	63
10	Chlorobenzene	Dimethyl	 **177**	24[c]

Conditions: 20 mol% $In(OTf)_3$, 100 °C, 24 h, DCE, 5 equiv. Toluene.

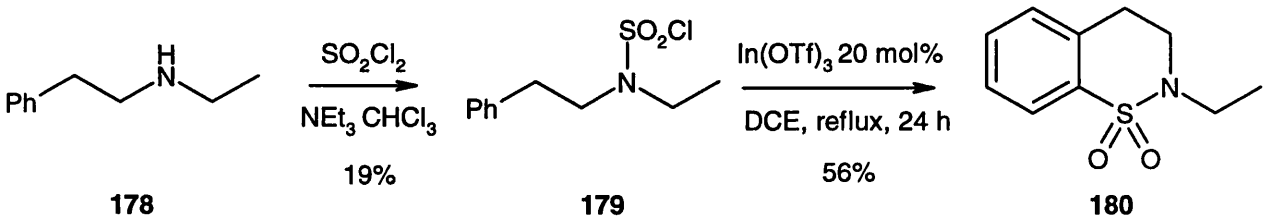
[a] *o*:*p*.

[b] α:β.

[c] 20 equiv. aromatic used as solvent.

Dimethyl, diethyl and piperidyl arylsulfonamides were produced in moderate to excellent yields. Purification of the crude products was typically by column chromatography. In some cases the regioisomers were separable by recrystallisation. The most activated aromatics, anisole and naphthalene, gave the highest yields in a mixture of *ortho* and *para* and α and β substitution respectively. Toluene and chlorobenzene reacted at the *para* position only.

In a further demonstration of the utility of the $In(OTf)_3$ catalysed sulfamoylation, an intramolecular reaction was carried out. Ethyl(phenethyl)sulfamoyl chloride **179** was prepared from (ethyl)phenethylamine **178** and sulfuryl chloride **166** (Scheme 86) and was purified by column chromatography. Analysis of the purified product showed that the three CH_2 signals of **178**, a quartet at δ2.67, a triplet at δ2.81 and a triplet at δ2.89, had shifted down field to give three new signals, a triplet at δ3.03 and two quartets at δ3.38 and δ3.54.



178 **179** **180**

Scheme 86

Indium triflate catalysed cyclisation of **179** gave product **180** in moderate yield, following column chromatography. Analysis of the ^1H NMR showed an accumulative total of four aromatic protons, with four sets of alkyl protons. The identity of the compound was confirmed by a high resolution mass spectrum of MH^+ 211.0666.

Such a process could not be achieved through traditional chlorosulfonation and amination as chlorosulfonation of **178** would generate the *para* sulfonyl chloride.

4.2.2 Mechanistic aspects

Whilst triflate/chloride exchange is likely to occur in the AgOTf-mediated sulfamoylation reaction (Table 4.2, entry 9), it is uncertain whether such a mechanism occurs at indium in the $In(OTf)_3$ catalysed process.

Triflic acid was shown to be a poor catalyst (Table 4.2, entry 10), and it is unlikely that the reaction is catalysed by adventitious triflic acid. In fact, the $In(OTf)_3$ catalysed sulfamoylation of toluene is not inhibited by 60 mol% 2,6-di-*tert*-butylpyridine added during the course of the reaction.

$In(NTf_2)_3$ and $InCl_3$ catalysis (Table 4.2, entry 3, 4) must proceed via co-ordination to the S-O bond, suggesting a similar co-ordination could be taking place with $In(OTf)_3$. However, the fact that $In(NTf_2)_3$ is less efficient than $In(OTf)_3$ (as observed in benzoylation and sulfonylation) suggests that triflate/chloride exchange may be occurring to some extent.

This chapter demonstrates the use of indium triflate in the first *catalytic* aromatic sulfamoylation reaction. This procedure offers a practical alternative to the traditional two step process of aromatic chlorosulfonation and subsequent reaction with an amine.

CHAPTER 5

CONCLUSIONS AND FURTHER WORK

5 Conclusions and Further Work

This thesis has shown indium(III) salts to be efficient, cheap and environmentally friendly Lewis acids for a number of electrophilic aromatic substitution reactions. Chapter 1 discuses the use of indium(III) Lewis acids as catalysts in a wide range of reactions, an area that has received considerable interest over recent years. Their remarkable stability to water allows the use of water as a solvent and the recycling of the catalyst on work-up.

Chapter 2 details the indium(III) catalysed acylation, benzoylation and sulfonylation of aromatics. Traditional Lewis acid promoters for these reactions are used in stoichiometric quantities, presenting serious waste problems. Low catalyst loadings of indium triflate in combination with lithium perchlorate catalyse the acylation of activated aromatics. Aqueous recycling of the indium and lithium salts was achieved without loss of activity. The benzoylation and sulfonylation of activated and deactivated aromatics was achieved using indium triflate. A high temperature ligand exchange process, generating benzoyl and sulfonyl triflates, is believed to be responsible for the excellent catalytic activity of indium triflate. The use of indium triflamide for such reactions is limited to activated aromatics.

The third chapter demonstrates indium triflate and indium triflamide as catalysts for aromatic nitration. In an environmentally friendly process, where water is the only by-product, indium(III) salts catalysed the nitration of activated and deactivated aromatics including benzoic acid derivatives and halobenzenes. The catalysts can be recycled and reused without loss of activity.

Finally, Chapter 4 demonstrates the use of indium triflate in the first catalytic aromatic sulfamoylation. Dialkylarylsulfonamides are formed in moderate to good yields, and both inter- and intramolecular sulfamoylations are possible. Other Lewis acids tested were inefficient. There is still further scope within this reaction particularly in the introduction of the SO_2NH_2 moiety.

Further Work

The utility of the ligand exchange process has still to be fully explored. In essence, any process where the generation of a triflate species in place of the corresponding chloride is beneficial could be investigated. Applications may be found in other electrophilic aromatic substitution reactions and even transition metal-mediated processes.

Whilst effective recycling of the indium catalyst has been achieved using aqueous extraction of the reaction mixture (for acylation and nitration), it is not applicable for sulfonylation, benzoylation and sulfamoylation. This is due to the formation of sulfonic and benzoic acids which also dissolve in the aqueous phase on work-up, contaminating the catalyst. In order to solve this problem, a fluorous soluble indium catalyst was synthesised, with the aim of carrying out electrophilic aromatic substitution reactions in a fluorous biphase.

Trends towards 'green chemistry' have led to the introduction of methods with low environmental impact. Among these methods, homogeneous catalysis in biphase

systems with one fluorous phase has attracted the attention of organofluorine chemists.[144] The fluorophilic properties of catalysts for fluorous biphase catalysis (FBC) are mostly provided by attached polyfluorinated ligands.

Basic structural requirement that provides sufficient fluorophilic properties of the catalysts is the overall fluorine content in the molecule, which should exceed 60%. Attempts to provide this high fluorine content by extending the length of a single fluorinated chain lead to inferior solubility in both phases employed. This results in the need for fluorous catalysts with multiple fluorinated chains.

The metal salts of the longer chain (C_4F_9 and C_8F_{17}) homologues of the triflamide and triflide anions allow access to catalysts suitable (by their high fluorine content) for fluorous phase or fluorous biphasic catalysis. Mikami and co-workers reported the use of $Yb[N(SO_2C_4F_9)_2]_3$ as a catalyst for Friedel-Crafts, Diels-Alder and esterification reactions in a fluoroaromatic, BTF.[145] Scandium and Ytterbium tris(perfluorobutanesulfonyl)methide complexes showed enhanced catalytic activity in the Friedel-Crafts acylation (in BTF), Diels-Alder reaction and Meerwein-Pondorf-Verley reductions (in organic solvents).[146] Ytterbium tris(perfluorobutanesulfonyl)methide, in combination with cyclodextrin-copolymer is an excellent catalyst for Diels-Alder and Mukaiyama aldol reactions in water.[147]

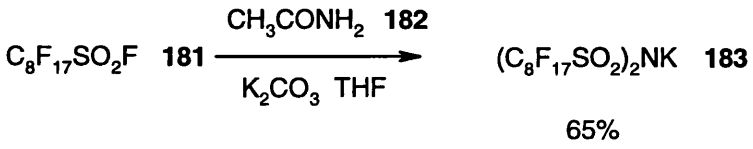
During the course of our studies, Barrett and co-workers reported the use of ytterbium tris(perfluoralkanesulfonyl)methide catalysts for fluorous phase acylation.[148] With sufficient fluorous content, the reactions could be run under a fluorous biphasic regime where the catalyst is recycled and re-used by extraction with

perfluoromethyldecalin. Mikami's group also reported scandium(III) tris(perfluorooctanesulfonyl)methide as a catalyst for fluorous phase Friedel-Crafts acylation, Diels-Alder, Mukaiyama aldol and esterification.[149]

Indium bis(perfluorooctanesulfonyl)amide

We sought to synthesise an indium(III) catalyst with sufficiently high fluorine content to render it preferentially soluble in perfluorinated solvents. The indium(III) salt of the long chain (C_8F_{17}) homologue of the triflamide anion was calculated as having an overall fluorine content above 60%, the accepted threshold for fluorous phase solubility.

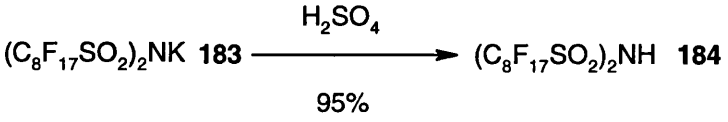
The synthesis of indium bis(perfluorooctanesulfonyl)amide, $In[N(SO_2C_8F_{17})_2]_3$, was synthesised in a straight-forward, three-step process from the corresponding perfluorooctanesulfonyl fluoride **181**. Using the methodology reported by Sogabe and co-workers,[150] acetamide **182** and sulfonyl fluoride **181** react in the presence an excess of potassium carbonate in refluxing THF to give potassium bis(perfluorooctanesulfonyl)amide **183**. Thus **182** was treated with one equivalent of **181** dropwise over 30 minutes. After 3 h, a further one equivalent of sulfonyl fluoride was added dropwise over 30 minutes and the reaction was stirred at reflux for a further 3 h. The reaction mixture was cooled, concentrated and dissolved in acetone. KF and K_2CO_3 were removed by filtration and the filtrate was concentrated. Washing the residue with ether removed any acetamide or **181**. Recrystallisation of the crude salt gave the desired amide **183** in 65% yield.



Scheme 86

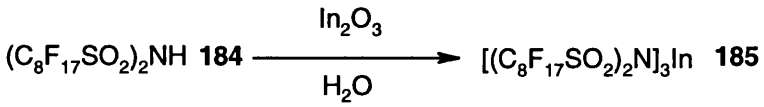
^{19}F NMR analysis showed 6 multiplets at –82.8, -116.01, -122.0, -123.1, -124.0 and –127.6, consistent with that found in the literature. Elemental analysis (C 17.2; N 2.0 and H 0.1%) did not coincide with calculated values (C 18.8; N 1.4 and H 0.0%). However, this is due to the product being an inflammable metal salt with high fluorine content. The values were, however, consistent with those found in the literature (C 17.3; N 2.2 and H 0.1%).[150]

Vacuum sublimation of a mixture of amide **183** from concentrated sulfuric acid proceeded smoothly at 100 °C and 0.7 mm Hg, to afford bis(perfluorooctanesulfonyl)imide, $(C_8F_{17}SO_2)_2NH$ **184** as a white solid in excellent yield (Scheme 87). ^{19}F NMR analysis showed 6 multiplets at –80.9, -114.9, -120.7, -122.0, -122.8 and –126.0, together with the appearance of a super-acidic N-H stretch at 3500 cm^{-1} in the infrared spectrum.



Scheme 87

Treatment of a suspension of indium oxide in water with an aqueous solution of **184** was followed by heating to reflux for 24 h. The suspension was observed to dissolve overnight. Concentration of the cooled solution gave a white solid, which was dried under high vacuum for 48 h to give indium(III) bis(perfluorooctanesulfonyl)amide as a off white solid in high yield (Scheme 88).

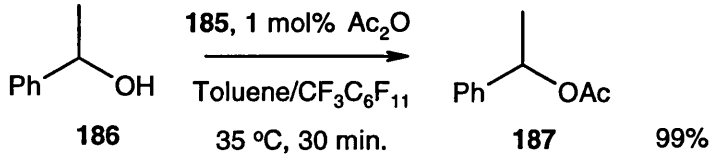


Scheme 88

Indium bis(perfluorooctanesulfonyl)amide in Catalysis

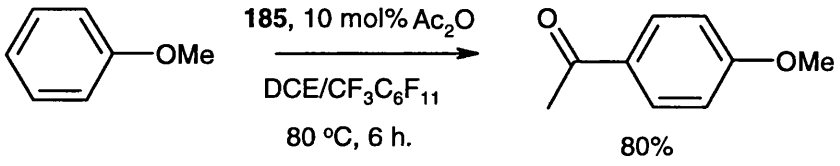
185 was found not to be fully soluble in perfluorinated solvents giving a white suspension. However, it was found to remain in the fluorous phase of a fluorous/organic biphase. We decided to investigate the use of **185** in fluorous biphasic catalysis.

Initial studies were directed towards the acylation of alcohols, a more facile transformation than the acylation of arenes. Thus, the acylation of *sec*-phenethyl alcohol **186** was acylated using acetic anhydride in the presence of 1 mol% **185** at 30 °C for 35 minutes in a biphasic system of perfluoromethylcyclohexane and toluene, to give 1-acetoxy-1-phenylethane **187** in high yield (Scheme 89). On cooling, the fluorous phase was separated and reused in further acylations without loss of catalytic activity.



Scheme 89

The use of **185** in Friedel-Crafts acylation was subsequently investigated. The acylation of anisole with acetic anhydride in the presence of 10 mol% **185** was studied under biphasic conditions (DCE/perfluoromethanecyclohexane). After 6h at 80 °C, 4-methoxyacetophenone was recovered in 80% yield (Scheme 90). However, recycling of the catalyst proved problematic, as, on cooling, the catalyst became suspended at the interface of the two layers. What was recovered of the catalyst was reused under the same conditions and gave only 20% conversion to the ketone.



Scheme 90

Under the same conditions, the sulfonylation of anisole with benzenesulfonyl chloride gave no reaction. Thus, indium bis(perfluoroctanesulfonyl)amide was synthesised through a facile, three-step process from the corresponding sulfonyl fluoride. Whilst effective for biphasic heteroatom acylation it was ineffective as a recyclable Friedel-Crafts catalyst.

CHAPTER 6

EXPERIMENTAL

6 Experimental

6.1 General Experimental

Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Apparatus, needles and syringes were oven-dried and cooled. General solvents were distilled before use. Diethyl ether, hexane, THF, and toluene were distilled from sodium wire. Nitromethane, DCE, DCM and MeCN were distilled from CaH_2. All solvents were stored in the presence of 4 Å molecular sieves.

TLC using commercially available aluminium plates coated with Merck Kieselgel 60 GF_{254} silica monitored all reactions. Visualisation of these plates was by 254-nm light or with $KMnO_4$ / Vanillin dips followed by heating. Organic layers were dried with $MgSO_4$ and evaporated with a Büchi evaporator. Further evaporation was carried out on a high-vacuum line where necessary. Flash chromatography was carried out on Kieselgel 60 H silica.

Proton (δ ^1H) NMR spectra were run in $CDCl_3$ using either a Brüker AC- 250 (250 MHz), Brüker WH- 300 (300 MHz), Brüker WH- 400 (400 MHz), Jeol (270 MHz) or Jeol (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm) as internal standard. Coupling constants (*J*) are given as Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (b). Carbon-13 (δ ^{13}C) NMR spectra were run in $CDCl_3$ at 100 MHz unless otherwise stated. Spectra were recorded using a Brucker AC- 250 (250 MHz), Brucker WH-300 (300 MHz), Brucker WH- 400 (400 MHz), Jeol (270 MHz) or Jeol (400 MHz) instrument.

Mass-spectra, including high resolution spectra, were recorded on a Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+) ionisation and/or Fast Bombardment (FAB+) ionisation.

Visualisation dips: Preparation of potassium permanganate: 0.5g $KMnO_4$ in 100 ml water. Preparation of vanillin: 3g vanillin / 100 ml EtOH + 3 ml conc. H_2SO_4 / 100 ml EtOH.

Preparation of indium(III) bis(trifluoromethylsulfonyl)amide

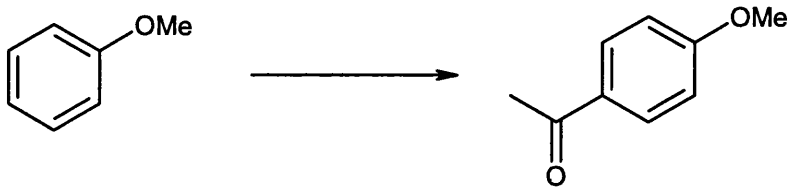
A suspension of indium(III) oxide (0.3 mmol) in water (20 ml) was treated with bis(trifluoromethylsulfonyl)imide (1.8 mmol). After heating to reflux for 24 h, the reaction mixture was cooled and filtered to remove unreacted indium(III) oxide. Solvents were removed under vacuum to provide indium(III) bis(trifluoromethylsulfonyl)amide as a colourless solid (isolated yield 99%, 0.285 g). δ_C (75.5 MHz, D_2O): 121.6. δ_F (376 MHz, $CDCl_3$): -78.95. *m/z* (ES^-) 282 (NTf_2^-, 11%), 280 (NTf_2^-, 100).

6.2 Acylation of Aromatics

General procedure for the acylation of aromatics

To a stirred solution of indium catalyst (0.06 mmol) and lithium perchlorate (6 mmol) in dry nitromethane (5 ml) under nitrogen at 50 °C was added the corresponding aromatic (6 mmol). After 10 min at 50 °C acetic anhydride (9 mmol) was added and the reaction was stirred until complete as judged by TLC. The solution was quenched with water (5 ml), and the product extracted with dichloromethane (3 x 5 ml). The organic layers were washed with brine (25 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Further purification by column chromatography (light petroleum: ethyl acetate, 9:1) gave the corresponding aromatic ketone.

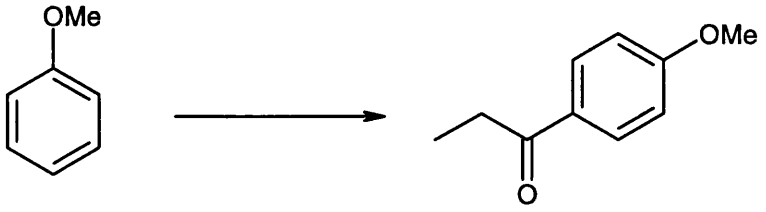
4-Methoxyacetophenone 97[151]



97

Anisole (6 mmol) was acylated using the general procedure to provide 4-methoxyacetophenone as off colourless needles (isolated yield 96%, 0.864 g). The data for 4-methoxyacetophenone was consistent with that found in the literature. IR (neat) 1720 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.58 (s, 3H), 3.87 (s, 3H), 6.93 (d, *J* 7.0, 2H), 7.92 (d, *J* 7.0, 2H). δ_C (75.5 MHz, $CDCl_3$): 26.7, 55.8, 114.0, 130.6, 130.9, 163.8, 197.2. *m/z* (EI^+) 150.2 (M^+, 100). Elemental analysis (Found: C, 71.8; H, 6.62. $C_9H_{10}O_2$ requires C, 72.0; H, 6.71 %).

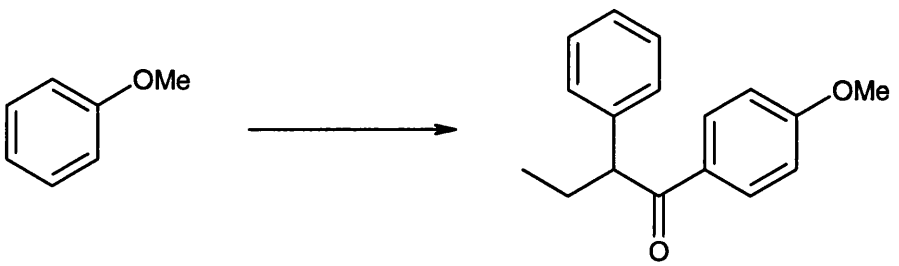
4-Methoxypropanophenone 100[152]



100

Anisole (6 mmol) was acylated with propanoic anhydride (9 mmol) using the general procedure to provide 4-methoxypropanophenone as a crystalline solid (isolated yield 99 %, 0.974 g). The data for 4-methoxypropanophenone was consistent with that found in the literature. IR (nujol) 1694 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.23 (t, *J* 7.0, 3H), 2.94 (q, *J* 7.0, 2H), 3.85 (s, 3H), 6.93 (d, *J* 9.0, 2H), 7.92 (d, *J* 9.0, 2H). δ_C (75.5 MHz, $CDCl_3$): 8.4, 31.41, 55.4, 113.7, 130.2, 131.1, 163.3, 199.5. *m/z* (EI^+) 164.1 (M^+, 100). Elemental analysis (Found: C, 72.9; H, 7.35. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.27 %).

1-(4-Methoxyphenyl)-2-phenyl-butanone 102[153]

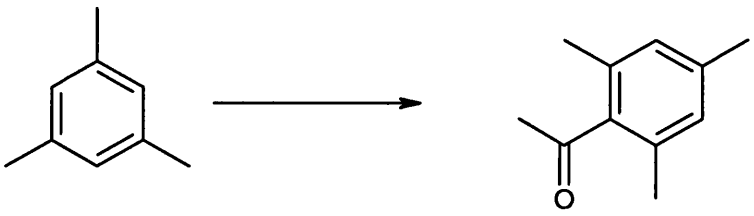


102

(2-Phenyl)-butanoic acid (20 mmol) in dichloromethane (10 ml) was treated with oxalyl chloride (20 mmol) and stirred at 0 °C overnight. Solvent and excess oxalyl chloride were removed by evaporation *in vacuo*. Following addition of dry nitromethane (5 ml), indium triflate (0.2 mmol) and lithium perchlorate (20 mmol) the

reaction mixture was heated to reflux for 10 min. Anisole (20 mmol) was added and the reaction mixture was maintained at reflux for 1 h. The solution was quenched with water (5 ml), and the product extracted with dichloromethane (3 x 10 ml). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Further purification by column chromatography (light petroleum: ethyl acetate, 9:1) afforded 1-(4-methoxyphenyl)-2-phenyl-butanone as a colourless powder (isolated yield 76%, 3.67 g). mp 44-45 °C (lit.[153] 46 °C). δ_H (75.5 MHz, $CDCl_3$): 0.90 (t, *J* 7.3, 3H), 1.70-2.30 (m, 2H), 4.40 (t, *J* 7.3, 1H), 6.86 (d, *J* 8.0, 2H), 7.16-7.31 (m, 5H), 7.96 (d, *J* 8.0, 2H). δ_C (300 MHz, $CDCl_3$): 12.3, 27.1, 55.1, 55.4, 113.6, 126.8, 128.2, 128.8, 130.0, 130.9, 140.1, 163.2, 198.6. *m/z* (CI^+) 255.2 (M^+, 100%). Elemental analysis (Found: C, 80.4; H, 6.97. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.13 %).

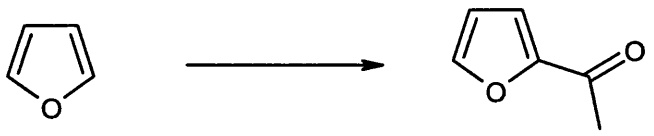
2,4,6-Trimethylacetophenone 104[154]



104

Mesitylene (6 mmol) was acylated using the general procedure to provide 2,4,6-trimethylacetophenone as colourless needles (isolated yield 99%, 0.962 g). The data for 2,4,6-trimethylacetophenone was consistent with that found in the literature. IR (neat) 1703 cm^{-1}.δ_H (270 MHz, $CDCl_3$): 2.21 (s, 6H), 2.24 (s, 3H), 2.48 (s, 3H), 6.83 (s, 2H). δ_C (75.5 MHz, $CDCl_3$): 19.1, 21.0, 32.3, 128.5, 132.3, 138.3, 139.9. *m/z* (EI^+) 162.1 (M^+, 100). Elemental analysis (Found: C, 80.7; H, 8.54. $C_{11}H_{14}O$ requires C, 81.44; H, 8.70 %).

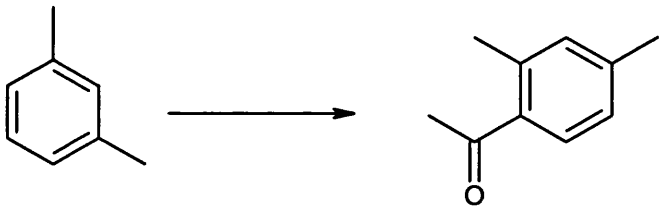
2-Acetylfuran 105[155]



105

Furan (6 mmol) was acylated using the general procedure to provide 2-acetylfuran as a clear oil (isolated yield 99%, 0.653 g). The data for 2-acetylfuran was consistent with that found in the literature. IR (neat) 1678 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.50 (s, 3H), 6.52 (dd, ^3J 4.0, ^3J 2.0, 1H), 7.19 (dd, ^3J 4.0, ^4J 0.9, 1H), 7.60 (dd, ^3J 2.0, ^4J 0.9, 1H). δ_C (63 MHz, $CDCl_3$): 25.6, 111.9, 117.0, 146.2, 152.5, 144.2. Elemental analysis (Found: C, 65.2; H, 5.70. $C_6H_6O_2$ requires C, 65.4; H, 5.50 %).

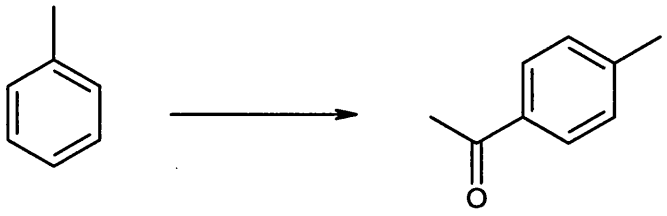
2,4-Dimethylacetophenone 106[156]



106

m-Xylene (6 mmol) was acylated using the general procedure to provide 2,4-dimethylacetophenone as a colourless powder (isolated yield 90%, 0.799 g). The data for 2,4-dimethylacetophenone was consistent with that found in the literature.IR (nujol) 1686 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.36 (s, 3H), 2.52 (s, 3H), 2.56 (s, 3H), 7.22-7.30 (m, 2H), 7.64 (dd, ^3J 8.0, 1H). δ_C (63 MHz, $CDCl_3$): 21.3, 21.6, 29.2, 126.3, 129.9, 132.9, 134.9, 138.8, 142.0, 200.8. *m/z* (EI$^+$) 148.0 (M^+, 100%). Elemental anaylsis (Found: C, 79.7; H, 8.30. $C_{10}H_{12}O$ requires C, 81.0; H, 8.15 %).

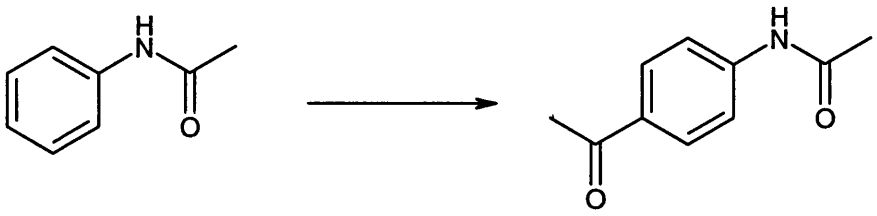
4-Methylacetophenone 107[157]



107

To a stirred solution of indium triflate (0.6 mmol) and lithium perchlorate (6 mmol) in dry nitromethane (5 ml) under nitrogen at reflux (oil bath 90°C) was added toluene (6 mmol). After 10 min at reflux acetic anhydride (9 mmol) was added and the reaction was stirred for 1 h. The solution was quenched with water (5 ml), and the product extracted with dichloromethane (3 x 5 ml). The organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude 4-methylacetophenone. Further purification by column chromatography (light petroleum: ethyl acetate, 9:1) gave the 4-methylacetophenone as a clear oil (isolated yield 82%, 0.659 g). The data for 4-methylacetophenone was consistent with that found in the literature. IR (nujol) 1692 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.34 (s, 3H), 2.52 (s, 3H), 7.19 (d, *J* 6.5, 2H), 7.79 (d, *J* 6.5, 2H). δ_C (63 MHz, $CDCl_3$): 21.5, 26.4, 128.4, 129.2, 134.8, 143.7, 197.5. *m/z* (EI^+) 134.0 (M^+, 100). Elemental analysis (Found: C, 80.5; H, 7.45. $C_9H_{10}O$ requires C, 80.6; H, 7.50 %).

4-Acylacetanilide 109[158]



109

To a stirred solution of indium triflate (0.04 mmol), lithium perchlorate (12 mmol) in dry nitromethane (2 ml) and acetic anhydride (1.6 mmol) under nitrogen at 50°C was added acetanilide (0.8 mmol). After the reaction had been stirred at 50°C for 24 h, the solution was quenched with water (5 ml), and the product extracted with dichloromethane (3 x 5 ml). The organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude 4-acylacetanilide. Purification by column chromatography (light petroleum: ethyl acetate, 9:1) gave the 4-acylacetanilide as colourless plates (74% yield, 0.105 mg). The data for 4-acylacetanilide was consistent with that found in the literature. mp 168-170°C (lit.[158] 169-171 °C). IR (neat) 1687 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.25 (s, 3H), 2.60 (s, 3H), 7.63 (d, *J* 8.8, 2H), 7.94 (d, *J* 8.8, 2H). δ_C (75.5 MHz, $CDCl_3$): 24.8, 26.5, 118.6, 130.0, 132.8, 142.6, 168.9, 196.1.

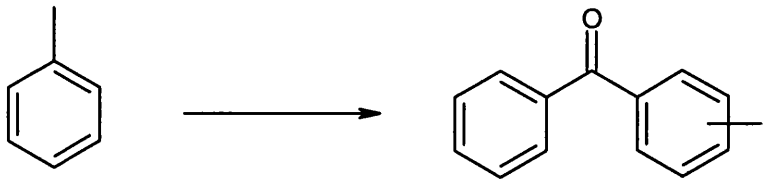
6.3 Benzoylation of Aromatics

General procedure for the benzoylation of aromatics

To a suspension of indium triflate (2.4 mmol) in the corresponding aromatic compound (48 mmol) at reflux was added benzoyl chloride (4.8 mmol). After a

further 24 h at reflux, 20 ml DCM was added and the reaction mixture was extracted with 1M HCl (3 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. Further purification by column chromatography (light petroleum: ethyl acetate, 9:1) gave the corresponding aromatic ketone.

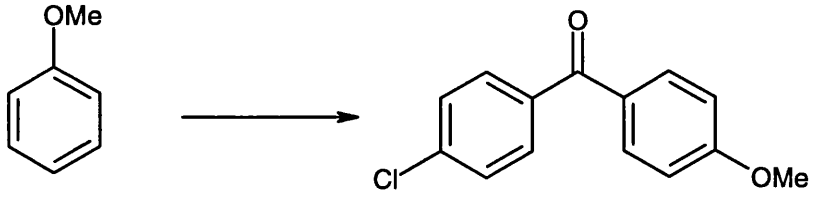
2- and 4-Methylbenzophenone 110[84]



110

Toluene (48 mmol) was benzoylated using the general procedure to provide 2- and 4-methylbenzophenone as a colourless oil (isolated yield 95%, 0.894 g). The data for 2- and 4-methylbenzophenone (12:88) was consistent with that found in the literature. IR (neat) 1710 cm^{-1}. δH (270 MHz, $CDCl_3$): 2.36 (s, 3H, 4-**110**), 2.52 (s, 3H, 2-**110**), 7.25-7.64 (m, 9H). δ_C (75.5 MHz, $CDCl_3$): (4-**110**) 22.1, 128.6, 129.4, 130.3, 130.7, 132.6, 135.3, 138.3, 196.9; (2-**110**) 19.9, 125.1, 128.4, 130.0, 130.2, 130.9, 133.1, 136.6, 137.7, 138.6, 198.4.

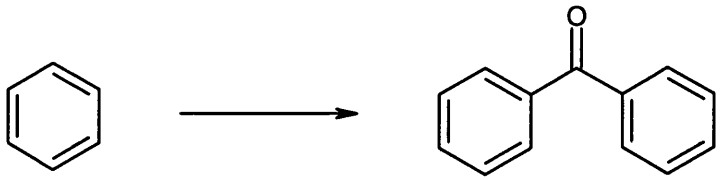
2- and 4-(Methoxy)-4'-chlorobenzophenone 111[159]



111

Anisole (50 mmol) was benzoylated with 4-chlorobenzoyl chloride (5 mmol) using the general procedure to provide 2- and 4-(methoxy)-4'-chlorobenzophenone (8:92) as a colourless oil (isolated yield 99%, 2.44 g). Recrystallisation of crude product with anisole: light petroleum gave 4-(methoxy)-4'-chlorobenzophenone as colourless needles (isolated yield 86%, 2.11 g) The data for 4-(methoxy)-4'-chlorobenzophenone was consistent with that found in the literature. mp 127-128 °C (lit.[159] 128-129 °C). IR (neat) 1653 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 3.89 (s, 3H), 6.96 (d, *J* 9.0, 2H), 7.48 (d, *J* 8.7, 2H), 7.73 (d, *J* 8.7, 2H), 7.80 (d, *J* 9.0, 2H). δ_C (75.5 MHz, $CDCl_3$): 55.9, 114.1, 128.9, 130.2, 131.6, 132.8, 136.9, 138.7, 163.8, 194.7. *m/z* (EI^+) 246.0 (M^+, 100%). Elemental analysis (Found: C, 68.2; H, 4.52 %, $C_{14}H_{11}ClO_2$ requires: C, 68.2; H, 4.50 %).

Benzophenone 112[160]

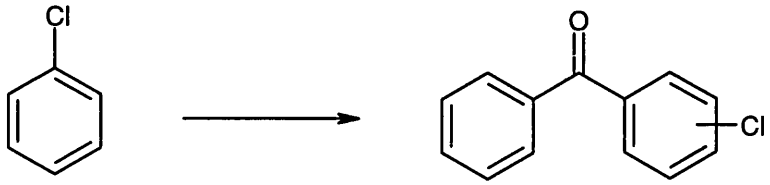


112

Benzene (48 mmol) was benzoylated using the general procedure to provide benzophenone as a colourless powder (isolated yield 79%, 0.690 g). The data for benzophenone was consistent with that found in the literature. IR (neat) 1659 cm^{-1}. δ_H

(300 MHz, $CDCl_3$): 7.43-7.50 (m, 2H), 7.54-7.62 (m, 1H), 7.75-7.80 (m, 2H). δ_C (75.5 MHz, $CDCl_3$): 127.8, 132.0, 137.1, 196.2.

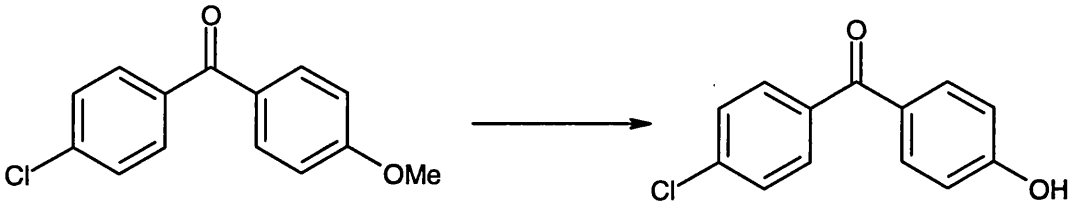
2- and 4- Chlorobenzophenone 113[160]



113

Chlorobenzene (48 mmol) was benzoylated using the general procedure to provide 2- and 4-chlorobenzophenone (1:9) as a colourless powder (isolated yield 79%, 0.690 g). The data for 2- and 4-chlorobenzophenone was consistent with that found in the literature. IR (neat) 1663 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 7.44-7.53 (m, 5H), 7.55-7.63 (m, 1H), 7.70-7.78 (m, 4H). δ_C (75.5 MHz, $CDCl_3$): 128.8, 129.0, 130.3, 131.9, 133.0, 137.6, 139.3, 195.9. *m/z* (EI^+) 216.0 (M^+, 100%).

(4-Hydroxy)-4'-chlorobenzophenone 114[161]

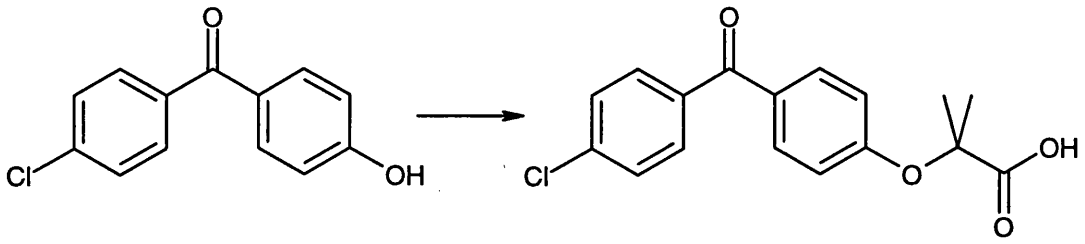


114

A suspension of 4-**111** (1.54 mmol) in glacial AcOH (8 ml) was flushed with nitrogen, heated until it became homogeneous, and then diluted with 48% HBr in H_2O (40 ml). The mixture was heated to reflux over 1 h, and after a further 30 min at reflux the reaction was complete by TLC. The cooled mixture was shaken with H_2) (200 ml) and extracted with DCM (3 x 30 ml). The organic fractions were dried ($MgSO_4$) and

concentrated to give (4-hydroxy)-4'-chlorobenzophenone as a red powder (isolated yield 99%, 0.36 g). The data for (4-hydroxy)-4'-chlorobenzophenone was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 6.15 (s, b, 2H), 6.90 (d, *J* 8.7, 2H), 7.48 (d, *J* 8.3, 2H), 7.70-7.78 (m, 4H). δ_C (75.5 MHz, $CDCl_3$): 115.6, 127.9, 128.7, 131.2, 132.7, 136.8, 137.1, 162.4, 193.1.

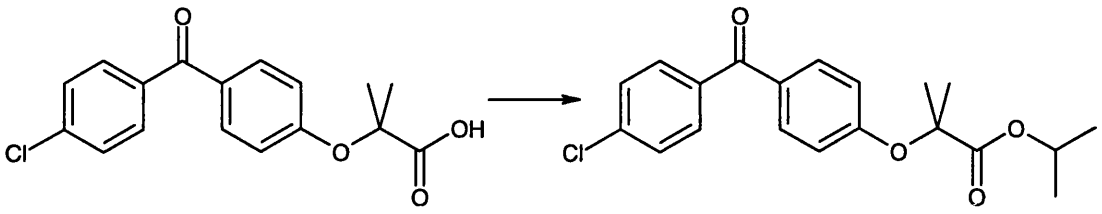
Fenofibric acid 115[162]



115

To a solution of (4-hydroxy)-4'-chlorobenzophenone (2.32 mmol) in acetone (10 ml) was added ground sodium hydroxide (15.3 mmol). The mixture was gently refluxed and chloroform (3.48 mmol) was added slowly to maintain boiling. After a further 4 h reflux, the reaction was cooled and concentrated *in vacuo*. The residue was diluted with 1M HCl (20 ml) and extracted with diethyl ether (2 x 10 ml). The organic layers were dried ($MgSO_4$), filtered and concentrated to yield the crude product as a solid. Recrystallisation (ethyl acetate/light petroleum) gave **115** as a colourless solid (isolated yield 76 %, 0.564 g). δ_H (300 MHz, $CDCl_3$): 1.72 (s, 6H), 6.96 (d, *J* 8.7, 2H), 7.47 (d, *J* 8.7, 2H), 7.70-7.80 (m, 4H).

Fenofibrate 116[162]



116

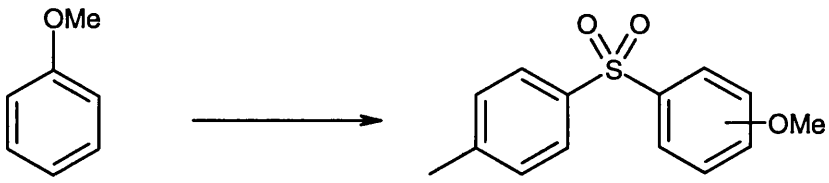
A suspension of **115** (0.74 mmol) in isopropanol (2 ml) was treated with concentrated sulfuric acid (0.1 ml) and heated to reflux for 3h. After cooling the reaction mixture was diluted with water (20 ml) and diethyl ether (20 ml). The aqueous phase was washed with diethyl ether (3 x 10 ml) and the combined organic phases were washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give Fenofibrate as colourless plates without further purification (isolated yield 86%, 0.230 g). The data for Fenofibrate was consistent with that found in the literature. mp 78 °C (lit.,[162] 80 °C); δ_H (300 MHz, $CDCl_3$): 1.21 (d, *J* 7.0, 6H), 1.65 (s, 6H), 5.10 (sep, *J* 7.0, 1H), 6.85 (d, *J* 8.7, 2H), 7.46 (d, *J* 8.7, 2H), 7.69-7.77 (m, 4H). δ_C (75.5 MHz, $CDCl_3$): 21.9, 25.7, 69.7, 79.8, 117.6, 128.9, 130.6, 131.6, 132.3, 136.8, 138.7, 160.1, 173.5, 194.6. *m/z* (EI^+) 360.1 (M^+, 100).

6.4 Sulfonylation of Aromatics

General procedure for the sulfonylation of activated aromatics

A 50 ml round-bottom flask was charged with indium triflate (0.32 mmol), aromatic (6.4 mmol) and sulfonyl chloride (3.2 mmol). The reaction mixture was stirred under nitrogen and heated to 120 °C until TLC showed complete consumption of sulfonyl chloride. The cooled reaction mixture was diluted with DCM (20 ml) and 1 M HCl (20 ml). The organic phases were dried ($MgSO_4$), filtered and concentrated *in vaccuo* to afford the crude product. Further purification by column chromatography (light petroleum: ethyl acetate, 4:1) gave the corresponding aromatic sulfone.

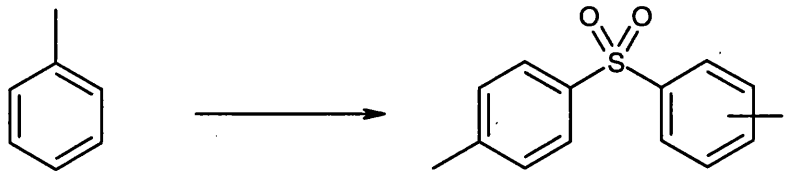
(Methoxyphenyl)-*p*-tolyl sulphone 117[163]



117

Anisole (6 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide 4- and 2-(methoxyphenyl)-*p*-tolyl sulphone (62:32) as a colourless powder (isolated yield 88 %, 0.692 g). The data for methoxyphenyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp (4-**117**) 104 °C (lit.,[163] 103 °C). IR (nujol) 1315, 1156 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.38 (s, 3H, methyl, 4-**117**), 2.40 (s, 3H, methyl, 2-**117**), 3.80 (s, 3H, 4-**117**), 3.85 (s, 3H, 2-**117**), 6.95-8.15 (m, 8H). δ_C (63 MHz, $CDCl_3$): (4-**117**) 21.9, 56.0, 115.0, 127.6, 129.9, 130.0. *m/z* (FAB^+) 263 (M^+, 100%). (Found 263.075, $C_{14}H_{14}O_3S$ requires 263.074).

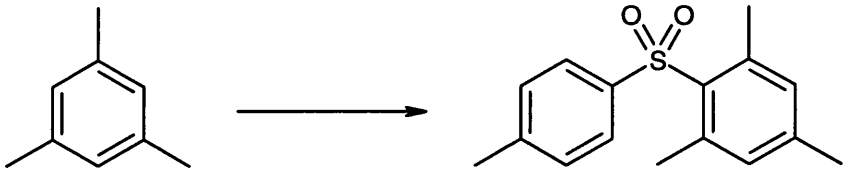
(Tolyl)-*p*-tolyl sulphone 118[164]



118

Toluene (6 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide 4- and 2-(tolyl)-*p*-tolyl sulphone (62:38) as a colourless powder (isolated yield 80 %, 0.590 g). The data for (tolyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp (4-**118**) 155 °C (lit.,[164] 155 °C). IR (nujol) 1310, 1160 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.39 (s, Me, 4-**118**), 2.40 (s, Me, 2-**118**), 7.21-8.19 (m, 8H, Ar). δ_C (63 MHz, $CDCl_3$): 20.3 (4-**118**), 21.9 (2-**118**), 126.6-133.3. *m/z* (FAB^+) 247 ($M^+ + H$, 100%). (Found $M^+ + H$, 247.079, $C_{14}H_{15}O_2S$ requires 247.079).

(2,4,6-Trimethyl)-*p*-tolylsulfone 119[164]

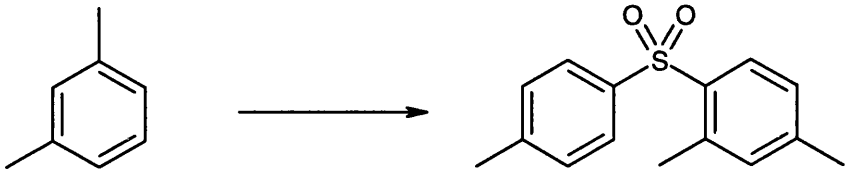


119

Mesitylene (6 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide (2,4,6-trimethyl)-*p*-tolyl sulphone as a colourless powder (isolated yield 78 %, 0.641 g). The data for (2,4,6-trimethyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp 119 °C (lit.,[164] 117 °C); IR (nujol) 1310, 1155 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.62 (s, 3H), 2.73 (s, 3H), 2.92 (s, 6H), 7.59 (m, 2H), 7.59 (s, 2H), 8.00 (m, 2H). δ_C (63 MHz, $CDCl_3$): 21.4, 22.0, 23.2, 126.5,

129.6, 132.3. *m/z* (FAB$^+$) 275 (M$^+$ + H, 100%). (Found 275.110 $C_{16}H_{19}O_2S$ requires 275.111).

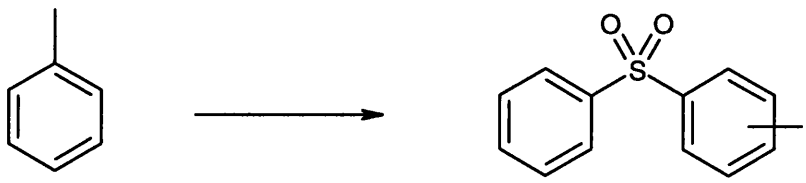
(2,4-Dimethyl)-*p*-tolylsulfone 120[164]



120

m-Xylene (6 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide (2,4-dimethyl)-*p*-tolyl sulphone a solid (isolated yield 88%, 0.686 g). The data for (2,4-dimethyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp 48-49 °C (lit.,[165] 49 °C). IR (nujol) 1310, 1155 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.36 (s, 3H), 2.39 (s, 3H), 2.40 (s, 3H), 7.12-7.20 (m, 2H), 7.27 (d, *J* 8.8, 2H), 7.73 (d, *J* 8.8, 2H), 8.08 (dd, ^3J 8.7, 1H). δ_C (63 MHz, $CDCl_3$): 20.5, 21.7, 22.0, 127.2, 127.8, 129.7, 129.7, 133.5. *m/z* (FAB$^+$) 261 (M$^+$ + H, 100%). (Found 261.095 $C_{15}H_{17}O_2S$ requires 261.095).

Phenyltolylsulphone 121[164]

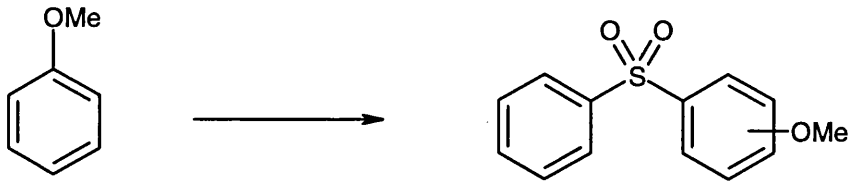


121

Toluene (6 mmol) was sulfonylated with benzenesulfonyl chloride (3 mmol) using the general procedure to provide 4- and 2-phenyltolylsulfone (63:37) as a colourless solid

(isolated yield 92 %, 0.640 g). The data for phenyltolylsulfone was consistent with that found in the literature. mp (4-**121**) 123-124 °C (lit.,[164] 125 °C). IR (nujol) 1299, 1145 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.40 (s, 3H, Me, 4-**121**), 2.44 (s, 3H, Me, 2-**121**), 7.23-8.22 (m, 9H, Aromatics). δ_C (63 MHz, $CDCl_3$): 20.3 (2-**121**), 21.9 (4-**121**), 126.3-133.8. *m/z* (FAB^+) 233 (M^+ + H, 100%). (Found 233.063 $C_{13}H_{13}O_2S$ requires 233.064).

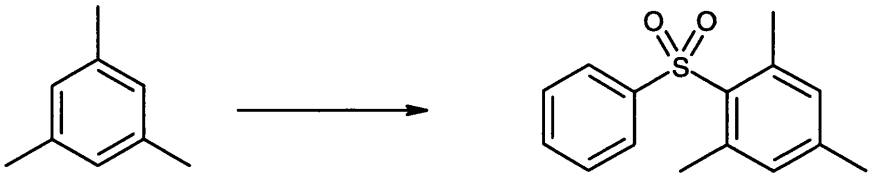
(Methoxyphenyl)phenylsulfone 122[120]



122

Anisole (6 mmol) was sulfonylated with benzenesulfonylchloride (3 mmol) using the general procedure to provide 4- and 2-(methoxyphenyl)phenylsulphone (60:40) as a colourless solid (isolated yield 98 %, 0.729 g). The data for (methoxyphenyl)phenylsulphone was consistent with that found in the literature. δ_H (270 MHz, $CDCl_3$): 3.76 (s, 3H, 2-**122**), 3.83 (s, 3H, 4-**122**), 6.90- 8.16 (m, 9H, aromatic). δ_C (63 MHz, $CDCl_3$): 56.0 (4-**122**), 56.1 (2-**122**), 112.7-135.7. *m/z* (FAB^+) 249 (M^+ + H, 100%). (Found 249.058 $C_{13}H_{13}O_3S$ requires 249.059).

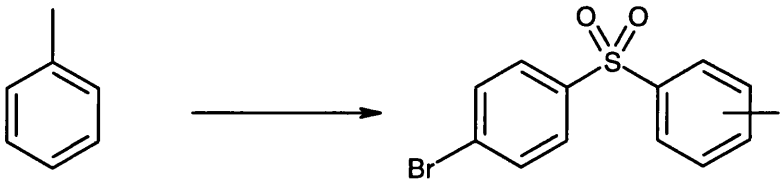
(2,4,6-Trimethylphenyl)phenylsulfone 123[166]



123

Mesitylene (6 mmol) was sulfonylated with benzenesulfonylchloride (3 mmol) using the general procedure to provide (2,4,6-trimethylphenyl)phenylsulphone a colourless solid (isolated yield 96 %, 0.749 g). The data for (2,4,6-trimethylphenyl)phenylsulphone was consistent with that found in the literature. mp 78-79 °C (lit.,[166] 80-81 °C). δ_H (270 MHz, $CDCl_3$): 2.30 (s, 3H, 4-Methyl), 2.60 (s, 6H, 2&6 Methyl), 6.94 (s, 2H), 7.50 (m, 3H), 7.79 (d, *J* 8.0, 2H). δ_C (63 MHz, $CDCl_3$): 21.0, 22.8, 126.2, 128.9, 132.2, 132.6. *m/z* (FAB^+) 261 (M^+ + H, 100%). (Found 261.095; $C_{15}H_{17}O_2S$ requires 261.095).

(4-Bromophenyl)tolylsulfone 124[120]

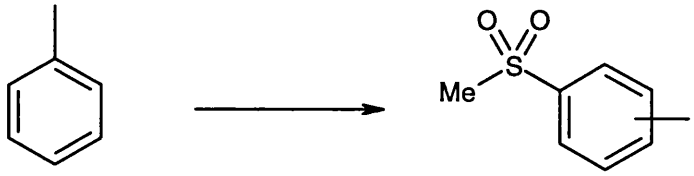


124

Toluene (6 mmol) was sulfonylated with 4-bromophenylsulfonylchloride (3 mmol) using the general procedure to provide 4- and 2-(4-bromophenyl)-tolylsulfone (60:40) as a solid (isolated yield 78 %, 0.728 g). The data for (4-bromophenyl)-tolylsulfone

was consistent with that found in the literature. mp (4-**124**) 134-135 °C (lit.,[120] 134-135 °C). δ_H (270 MHz, $CDCl_3$): 2.40 (s, 4-**124**), 2.44 (s, 4-**124**), 7.24-8.21 (m, aromatic). *m/z* (FAB^+) 313 (M^+ + H, (^{81}Br) 41.4%), 311 (M^+ + H, (^{79}Br) 40.6 %). (Found 310.975 (^{79}Br), $C_{13}H_{12}BrO_2S$ requires 310.974).

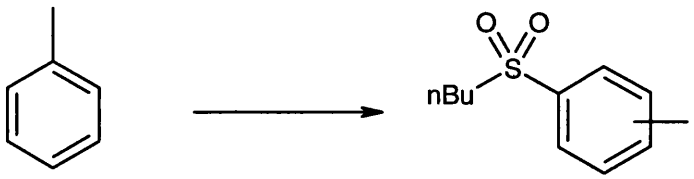
Methyltolylsulfone 125[167]



125

Toluene (15 mmol) was sulfonylated with methanesulfonylchloride (3 mmol) using the general procedure to provide 4-, 3- and 2-methyltolylsulfone (52:19:29) as a colourless oil (isolated yield 83 %, 0.423 g). The data for methyltolylsulfone was consistent with that found in the literature. δ_H (270 MHz, $CDCl_3$): 2.46 (s, ArMe, 4- & 3-**125**), 2.73 (s, ArMe, 2-**125**), 3.04 (s, SO_2Me, 4-**125**), 3.05 (s, SO_2Me, 3-**125**), 3.09 (s, SO_2Me, 2-**125**), 7.34-8.06 (m, ArH). *m/z* (FAB^+) 171 (M^+ + H, 100%). (Found 171.047, $C_8H_{11}O_2S$ requires 171.048).

_n_-Butyltolylsulfone 126[120]



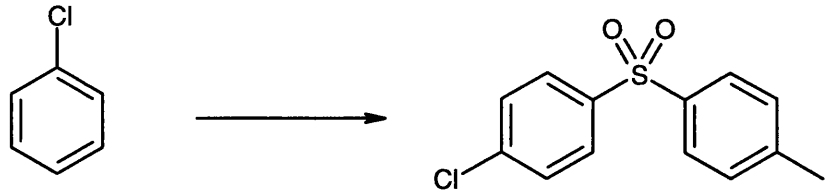
126

Toluene (15 mmol) was sulfonylated with _n_-butanesulfonylchloride (3 mmol) using the general procedure to provide 4-, 3- and 2-_n_-butyltolylsulfone (50:15:35) as a colourless oil (isolated yield 97 %, 0.617 g). The data for _n_-butyltolylsulfone was consistent with that found in the literature. δ_H (270 MHz, $CDCl_3$): 0.885 (m, Alkyl CH_3), 1.34-1.72 (m, Alkyl CH_2), 2.36 (s, ArMe, 3-**126**), 2.46 (s, ArMe, 4-**126**), 2.70 (s, ArMe, 2-**126**), 3.03-3.15 (m, SO_2CH_2), 7.19-8.01 (m, aromatic). _m/z_ (FAB^+) 213 ($M^+ + H$, 100%). (Found 213.096, $C_{11}H_{17}O_2S$ requires 213.095).

General procedure for the sulfonylation of haloaromatics

A 50 ml round-bottomed flask was charged with indium triflate (0.636 mmol), aromatic (15.9 mmol) and sulfonyl chloride (3.18 mmol). The reaction mixture was stirred under nitrogen and heated to 120 °C until TLC showed complete consumption of sulfonyl chloride. The cooled reaction mixture was diluted with DCM (20 ml) and 1 M HCl (20 ml). The organic phases were dried ($MgSO_4$), filtered and concentrated _in vaccuo_ to afford the crude product. Further purification by column chromatography (light petroleum: ethyl acetate, 4:1) gave the corresponding aromatic sulfone.

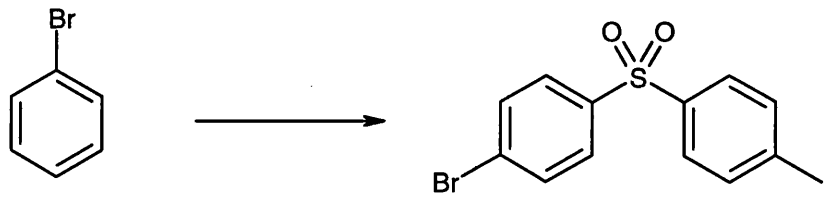
(4-Chlorophenyl)-*p*-tolylsulfone 127[167]



127

Chlorobenzene (15 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide (4-chlorophenyl)-*p*-tolyl sulphone a colourless powder (isolated yield 74 %, 0.592 g). The data for (4-chlorophenyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp 120 °C (lit.[167] 119-120 °C). IR (nujol) 1331, 1161 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.40 (s, 3H), 7.31 (d, *J* 7.8, 2H), 7.46 (d, *J* 8.0, 2H), 7.80 (d, *J* 7.8, 2H), 7.86 (d, *J* 8.0, 2H). δ_C (63 MHz, $CDCl_3$): 22.0, 127.9, 129.1, 129.7, 130.2. *m/z* (FAB$^+$) 269 (M^+ + H (^{37}Cl) 38%), 267 (M^+ + H (^{35}Cl) 100). (Found 267.025 (^{35}Cl), $C_{13}H_{12}ClO_2S$ requires 267.025).

(4-Bromophenyl)-*p*-tolylsulfone 128[120]

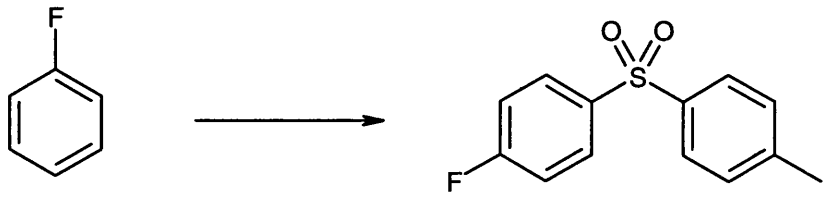


128

Bromobenzene (15 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide (4-bromophenyl)-*p*-tolyl sulphone as colourless needles (isolated yield 71 %, 0.662 g). The data for (4-bromophenyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp 137 °C (lit.,[120] 135-136 °C). IR (nujol)

1314, 1152 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 2.55 (s, 3H), 7.45 (d, *J* 8.6, 2H), 7.77 (d, *J* 8.0, 2H), 7.92 (d, *J* 8.0, 2H), 7.95 (d, *J* 8.6, 2H). δ_C (63 MHz, $CDCl_3$): 22.0, 127.9, 129.2, 130.2, 132.7. *m/z* (FAB^+) 313 ($M^+ + H$ (^{81}Br) 41.4%), 311 ($M^+ + H$ (^{79}Br) 40.6; (Found 310.975 (^{79}Br), $C_{13}H_{12}BrO_2S$ requires 310.974).

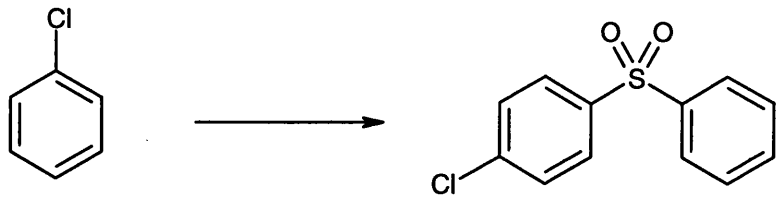
(4-Fluorophenyl)-*p*-tolylsulfone 129[168]



129

Fluorobenzene (15 mmol) was sulfonylated with tosyl chloride (3 mmol) using the general procedure to provide (4-fluorophenyl)-*p*-tolyl sulphone a colourless powder (isolated yield 66 %, 0.495 g). The data for (4-fluorophenyl)-*p*-tolyl sulphone was consistent with that found in the literature. mp 94 °C (lit.,[168] 95 °C). δ_H (270 MHz, $CDCl_3$): 2.40 (s, 3H), 7.16 (d, *J* 8.0, 2H), 7.31 (d, *J* 8.0, 2H), 7.81 (d, *J* 8.0, 2H), 7.94 (d, *J* 8.0, 2H). δ_C (63 MHz, $CDCl_3$): 22.0, 128.0, 130.2, 130.4, 130.5. *m/z* (FAB^+) 251 ($M^+ + H$, 100%). (Found 251.054, $C_{13}H_{12}FO_2S$ requires 251.054).

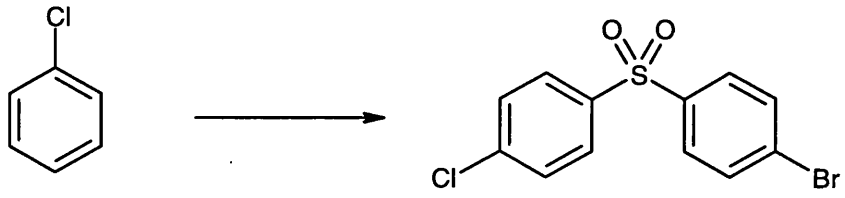
(4-Chlorophenyl)phenylsulfone 130[120]



130

Chlorobenzene (15 mmol) was sulfonylated with benzenesulfonyl chloride (3 mmol) using the general procedure to provide (4-chlorophenyl)phenylsulphone as a colourless powder (isolated yield 84 %, 0.636 g). The data for (4-chlorophenyl)phenylsulphone was consistent with that found in the literature. mp 91 °C (lit.,[120] 91-92 °C). IR (nujol) 1318, 1152 cm^{-1}. δ_H (270 MHz, $CDCl_3$): 7.50 (m, 4H), 7.58 (m, 1H), 7.82 (m, 2H), 7.93 (m, 2H). δ_C (63 MHz, $CDCl_3$): 127.8, 129.3, 129.6, 129.8, 133.6. *m/z* (FAB^+) 255 ($M^+ + H$ (^{37}Cl) 38%), 253 ($M^+ + H$ (^{35}Cl) 100). (Found 253.009 (^{35}Cl), $C_{12}H_{10}ClO_2S$ requires 253.009).

(4-Chlorophenyl)-4-bromophenylsulphone 131[169]



131

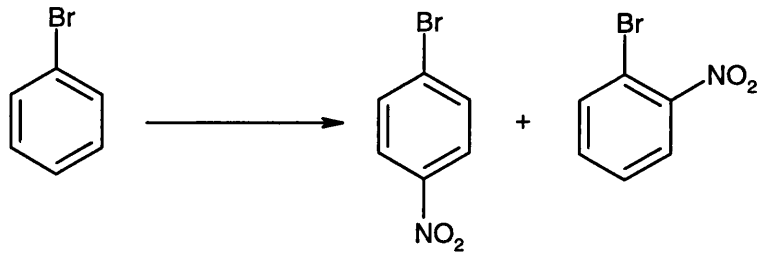
Chlorobenzene (15 mmol) was sulfonylated with 4-bromobenzenesulfonyl chloride (3 mmol) using the general procedure to provide (4-chlorophenyl)-4-bromophenylsulphone as a colourless powder (isolated yield 54 %, 0.537 g). The data for (4-chlorophenyl)-4-bromophenylsulphone was consistent with that found in the literature. mp 157 °C (lit.,[169] 157-158 °C). δ_H (270 MHz, $CDCl_3$): 7.49 (m, 2H), 7.66 (m, 2H), 7.79 (m, 2H), 7.86 (m, 2H). δ_C (63 MHz, $CDCl_3$): 129.1, 129.2, 129.8, 132.8. *m/z* (FAB^+) 335 ($M^+ + H$, ^{37}Cl and ^{81}Br), 333 ($M^+ + H$, ^{35}Cl and ^{81}Br and ^{37}Cl and ^{79}Br), 331 ($M^+ + H$, ^{35}Cl and ^{79}Br); (Found 330.920 (^{35}Cl and ^{79}Br), $C_{12}H_{10}ClO_2S$ requires 330.920).

6.5 Nitration of Aromatics

General procedure for the nitration of aromatics

To a suspension of the indium(III) salt (0.3 mmol) in dichloroethane (5 ml) was added nitric acid (3 mmol). After heating to reflux, the corresponding aromatic substrate (3 mmol) was added, and the reaction mixture was stirred at reflux for 18 h. The cooled reaction mixture was diluted with water (1 ml) and the organic phase was separated, dried ($MgSO_4$) and concentrated to give the crude nitroaromatic. Further purification by column chromatography (light petroleum: ethyl acetate, 9:1) gave the corresponding nitroaromatic product. The aqueous phase was evaporated to afford the indium salt as a colourless solid.

Nitrobromobenzene 138[170]

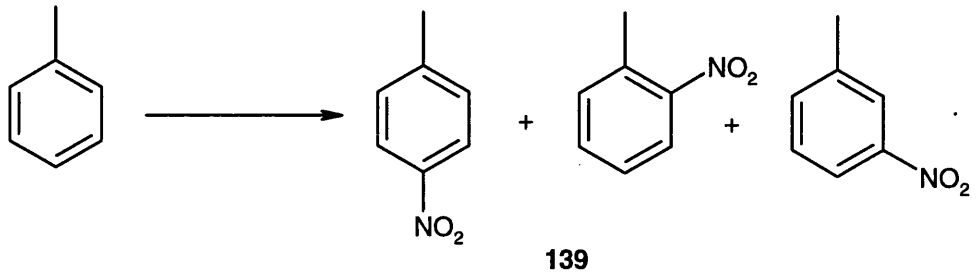


138

Bromobenzene (3 mmol) was nitrated using the general procedure to provide 2- and 4-nitrobromobenzene (39:61) as a yellow oil (isolated yield 98%, 0.864 g). The data for 2- and 4-nitrobromobenzene was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): (4-**138**) 7.73 (d, *J* 9.0, 2H), 8.12 (d, *J* 9.0, 2H). (2-**138**) 7.42-7.48 (m, 2H), 7.75 (ddd, ^3J 8.4, 1H), 7.85 (ddd, ^3J 8.4, 1H). δ_C (75.5 MHz, $CDCl_3$): (4-**138**) 125.2, 133.4; (2-**138**) 126.3, 128.0, 133.7, 135.6. *m/z* (EI^+) 203.0 (M^+ (^{81}Br) 41.2 %),

201.0 (M^+ (^{81}Br) 40.4 %). Elemental analysis (Found: C, 35.7; N, 6.9; H, 2.03. $C_6H_4BrNO_2$ requires C, 35.7; N, 6.9; H, 2.00 %).

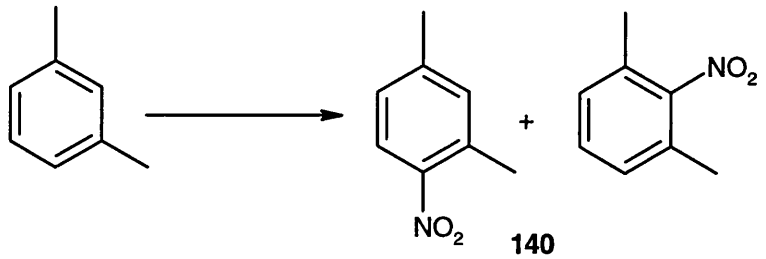
Nitrotoluene 139[170]



139

Toluene (3 mmol) was nitrated using the general procedure to provide 2-, 3- and 4-nitrotoluene (48:7:45) as a yellow oil (isolated yield 99%, 0.407 g). The data for 2-, 3- and 4-nitrotoluene was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 2.46 (s, 3H, 4-**139** and 3-**139**), 2.59 (s, 3H, 2-**139**), 7.20-8.10 (m, 4H, ArH). δ_C (75.5 MHz, $CDCl_3$): 20.3 (2-**139**), 21.2 (3-**139**), 21.6 (4-**139**), 120-149. *m/z* (EI^+) 137.1 (M^+ 100%). Elemental analysis (Found: C, 61.0; N, 9.96; H, 5.13; $C_7H_7NO_2$ requires C, 61.3; N, 10.21; H, 5.145 %).

Nitro-*m*-xylene 140[171]

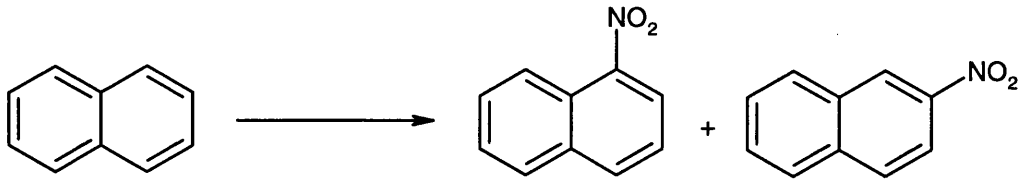


140

m-Xylene (3 mmol) was nitrated using the general procedure to provide 2- and 4-nitro-*m*-xylene (14:86) as a yellow oil (isolated yield 99%, 0.448 g). The data for 2- and 4-nitro-*m*-xylene was consistent with that found in the literature. δ_H (300 MHz,

$CDCl_3$): (4-**140**) 2.40 (s, 3H), 2.59 (s, 3H), 7.10-7.15 (m, 2H), 7.92 (dd, ^3J 8.8, 1H); (2-**140**) 2.32 (s, 6H), 7.09-7.13 (m, 3H). δ_C (300 MHz, $CDCl_3$): (4-**140**) 20.7, 21.3, 124.9, 127.5, 133.4, 133.8, 144.2, 146.9; (2-**140**) 17.4, 128.8, 129.5, 130.0. *m/z* (EI^+) 151.1 (M^+, 100%). Elemental analysis (Found: C, 63.7; N, 9.0; H, 6.00; $C_8H_9NO_2$ requires C, 63.6; N, 9.3; H, 6.00 %).

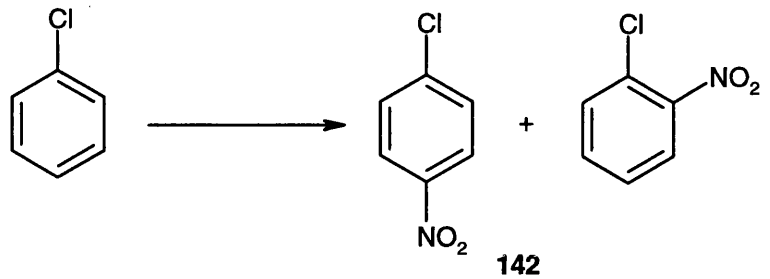
Nitronaphthalene 141[170]



141

Naphthalene (3 mmol) was nitrated using the general procedure to provide 1- and 2-nitronaphthalene (91:9) as a yellow solid (isolated yield 99%, 0.514 g). The data for 1- and 2-nitronaphthalene was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): (1-**141**) 7.52-7.60 (m, 1H), 7.61-7.68 (m, 1H), 7.72-7.78 (m, 1H), 7.94-7.99 (m, 1H), 8.13-8.16 (m, 1H), 8.23-8.27 (m, 1H), 8.55-8.60 (m, 1H); (2-**141**) 7.60-7.65 (m, 1H), 7.66-7.70 (m, 1H), 7.90-7.94 (2H), 7.96-8.02 (m, 1H), 8.17-8.20 (m, 1H), 8.75 (m, 1H). δ_C (75.5 MHz, $CDCl_3$): (1-**141**) 123.1, 124.0, 124.1, 125.1, 127.3, 128.6, 129.4, 134.3, 134.7 (2-**141**) 119.14, 124.46, 127.85, 127.92, 129.45, 129.69, 129.89, 131.88, 135.76, 145.45. *m/z* (EI^+) 173.0 (M^+, 100%).

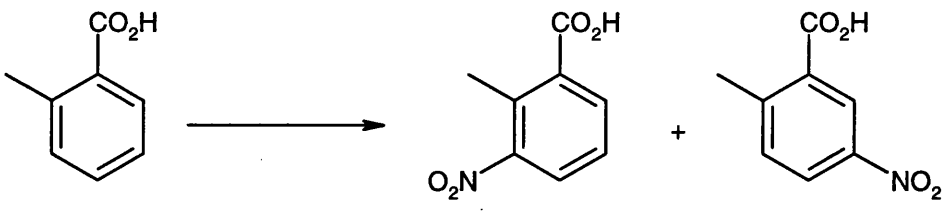
Nitrochlorobenzene 142[170]



142

Chlorobenzene (3 mmol) was nitrated using the general procedure to provide 2- and 4-nitrochlorobenzene (33:67) as a yellow powder (isolated yield 93%, 0.864 g). The data for 2- and 4-nitrochlorobenzene was consistent with that found in the literature. mp (4-nitrochlorobenzene) 80-81 °C (lit.,[172] 82 °C); δ_H (300 MHz, $CDCl_3$): (4-nitrochlorobenzene) 8.19 (d, *J* 9.4, 2H), 7.53 (m, *J* 9.4, 2H); (2-nitrochlorobenzene) 7.80 (ddd, ^3J 8.6, ^3J 8.6, 1H), 7.48-7.54 (m, 2H), 7.42 (ddd, ^3J 8.6, 1H). δ_C (300 MHz, $CDCl_3$): (4-nitrochlorobenzene) 125.33, 129.98, 141.78; (2-nitrochlorobenzene) 125.52, 126.90, 127.71, 131.88, 133.28, 148.10. *m/z* (EI) (Found: *M*+ 157.0 and 159.0, Expected *M*, 157.6). Elemental analysis (Found: C, 45.0; N, 8.7; H, 2.63; $C_9H_{10}O_2$ requires C, 45.7; N, 8.9; H, 2.56 %).

Nitro-2-methylbenzoic acid 143[173]

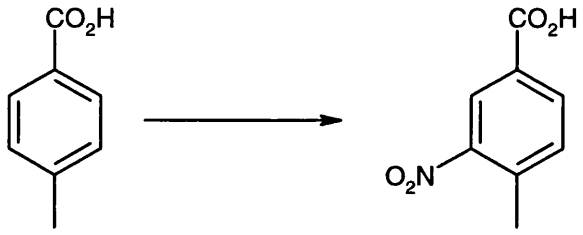


143

o-Toluic acid (1.9 mmol) was nitrated using the general procedure to 3- and 5-nitro-2-methylbenzoic acid (44:56) as a colourless powder (isolated yield 99%, 0.340 g). The

data for 3- and 5-nitro-2-methylbenzoic acid was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): (3-**143**) 2.79 (s, 3H), 7.48 (dd, ^3J 7.9, ^3J 8.0, 1H), 8.31 (dd, ^3J 7.9, ^4J 1.5, 1H), 8.94 (dd, ^3J 8.0, ^4J 1.5, 1H); (5-**143**) 2.71 (s, 3H), 7.47 (dd, ^3J 8.4, 1H), 7.90 (dd, ^3J 8.4, ^4J 2.6, 1H), 8.21 (dd, ^4J 2.6, 1H). δ_C (75.5 MHz, $CDCl_3$): (3-**143**). *m/z* (CI^+) 182.0 (M^+, 100%). *m/z* (ES^-) 180.0 (M^-, 100%). Elemental analysis (Found: C, 53.7; N, 7.4; H, 4.11. $C_8H_7NO_4$ requires C, 53.0; N, 7.7; H, 3.89 %).

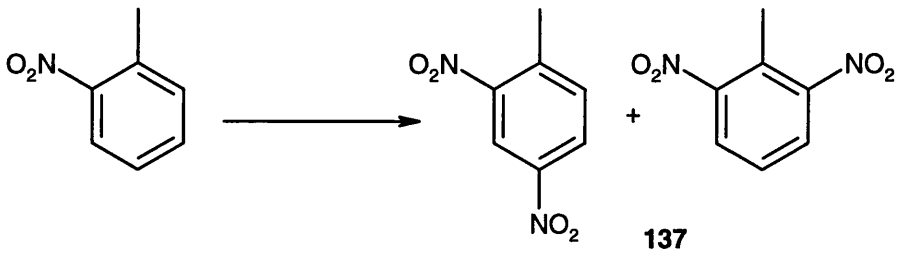
3-Nitro-4-methylbenzoic acid 144[174]



144

p-Toluic acid (1.64 mmol) was nitrated using the general procedure to 3-Nitro-4-methylbenzoic acid as a colourless powder (isolated yield 84 %, 0.25 g). The data for 3-nitro-4-methylbenzoic acid was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 2.70 (s, 3H), 7.50 (dd, ^3J 8.0, 1H), 8.22 (dd, ^3J 8.0, ^4J 1.6, 1H), 8.69 (dd, ^3J 1.6, 1H). δ_C (75.5 MHz, $CDCl_3$): 20.4, 126.6, 131.4, 134.3, 134.6, 139.3, 150.7, 167.5. *m/z* (ES^-) 180.0 (M^-, 100%).

2,4- and 2,6-dinitrotoluene 137[175]



137

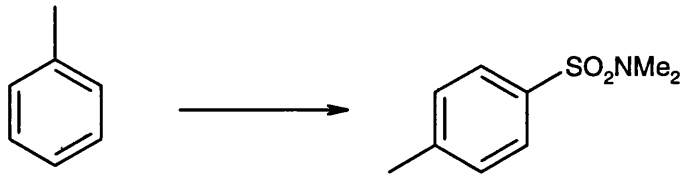
o-Nitrotoluene (3.00 mmol) was nitrated using the general procedure to 2,4- and 2,6-dinitrotoluene (65:35) as a yellow oil (isolated yield 31 %, 0.170 g). The data for 2,4- and 2,6- dinitrotoluene was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): (2,4-**137**) 2.75 (s, 3H), 7.66 (dd, ^3J 8.4, 1H), 8.38 (dd, ^3J 8.4, ^4J 2.3, 1H), 8.80 (dd, ^4J 2.3, 1H); (2,4-**137**) 2.56 (s, 3H), 7.58 (t, ^3J 8.1, 1H), 8.03 (d, ^3J 8.1, 2H). δ_C (75.5 MHz, $CDCl_3$): (2,4-**137**) 21.1, 120.6, 127.4, 134.5, 141.2, 146.7, 149.4. (2,6-**137**) 15.2, 127.6, 128.0, 1512.0. *m/z* (ES^-) 180.0 (*M*+, 100%).

6.6 Sulfamoylation of Aromatics

General Procedure for the Sulfamoylation of Arenes

To a suspension of indium triflate (0.2 mmol) and aromatic (5 mmol) in dry 1,2 dichloroethane (5 ml) with 4 Å molecular sieves was added *N,N*-dialkylsulfamoyl chloride (1 mmol) and the reaction mixture heated to reflux for 24 h. The cooled reaction mixture was diluted with DCM (20 ml) and washed with water (20 ml). The aqueous layer was back extracted with DCM (3 x 20 ml) and the combined organic fractions washed with saturated brine (25 ml), dried ($MgSO_4$) was concentrated *in vacuo* to afford the crude product. Further purification by column chromatography (light petroleum: ethyl acetate, 4:1) gave the corresponding product.

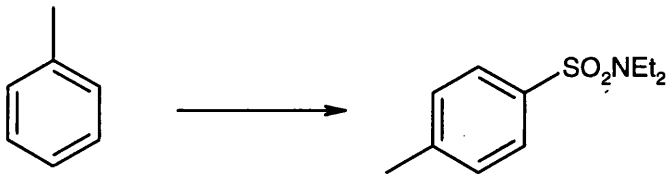
4,*N*,*N*-Trimethyl-benzenesulfonamide 163[176]



163

Toluene (5 mmol) was sulfamoylated with *N*,*N*-dimethylsulfamoyl chloride (1 mmol) using the general procedure to provide 4,*N*,*N*-trimethyl-benzenesulfonamide as colourless plates (isolated yield 86 %, 0.171 g). The data for 4,*N*,*N*-trimethyl-benzenesulfonamide was consistent with that found in the literature. mp 79-81 °C (lit.[176] 83-83.5 °C). δ_H (300 MHz, $CDCl_3$): 2.45 (s, 3H, Ar-Me), 2.68 (s, 6H, N-Me), 7.25 (d, *J* 8.7, 2H), 7.67 (d, *J* 8.7, 2H). δ_C (75.5 MHz, $CDCl_3$): 21.5, 38.0, 127.8, 129.6, 132.4, 143.5. %). *m/z* (EI^+): 199 (M^+, 22 %), 155 (M^+-NMe_2, 12), 91 (M^+-SO_2NMe_2, 100 %); (Found: 199.066. $C_9H_{13}NO_2S$ requires 199.067).

***N*,*N*-Diethyl-4-methylbenzenesulfonamide 167[142]**

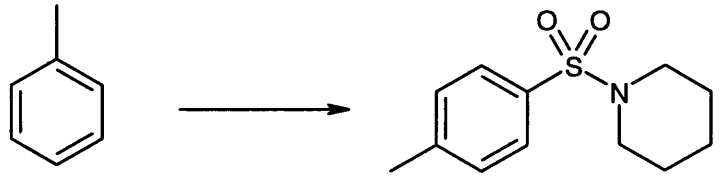


167

Toluene (5 mmol) was sulfamoylated with *N*,*N*-diethylsulfamoyl chloride (1 mmol) using the general procedure to provide *N*,*N*-diethyl-4-methylbenzenesulfonamide as a colourless oil (isolated yield 64 %, 0.14 g). The data *N*,*N*-diethyl-4-methylbenzenesulfonamide was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 1.08-1.16 (t, 6H, *J* = 7.2 Hz), 2.45 (s, 3H), 3.16-3.27 (q, 4H, *J* = 7.2

Hz), 7.27 (d, *J* 8.3, 2H), 7.68 (d, *J* 8.3, 2H). δ_C (75.5 MHz, $CDCl_3$): 14.2, 42.0, 127.0, 129.6, 137.4, 142.9. *m/z* (EI): 227 (M^+, 8 %), 212 (M^+-Me, 45), 155 (M^+-NEt_2, 47), 91 (M^+-SO_2Et_2, 100); (Found: M^+, 227.098. $C_{11}H_{17}NO_2S$ requires 227.098). Elemental analysis (Found: C, 57.9; N, 5.8; H, 7.40. $C_{11}H_{17}NO_2S$ requires C, 58.1; N, 6.2; H, 7.55%).

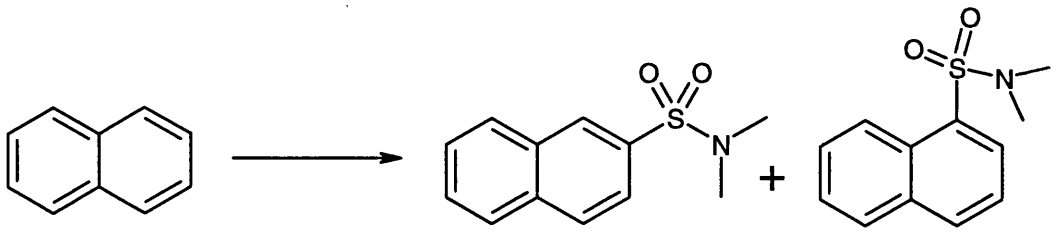
1-(Toluene-4-sulfonyl)-piperidine 168[142]



168

Toluene (5 mmol) was sulfamoylated with 1-chlorosulfonylpiperidine (1 mmol) using the general procedure to provide 1-(toluene-4-sulfonyl)-piperidine as a colourless powder (isolated yield 51 %, 0.12 g). The data for 1-(toluene-4-sulfonyl)-piperidine was consistent with that found in the literature. mp 96-98 (lit.[177] mp 96-98 °C). δ_H (300 MHz, $CDCl_3$): 1.38-1.43(m, 2H), 1.53-1.59 (m, 4H), 2.44 (s, 3H), 2.50-2.80 (m, 4H), 7.32 (d, *J* 8.7, 2H), 7.64 (d, *J* 8.7, 2H). δ_C (75.5 MHz, $CDCl_3$): 21.5, 23.5, 25.2, 46.9, 127.7, 129.5, 133.2, 143.3. Elemental analysis (Found: C, 60.2; H, 7.10; N, 5.6. $C_{12}H_{17}NO_2S$ requires C, 60.2; H, 7.15; N, 5.9 %). *m/z* (EI): 239 (M^+, 22 %), 155 (M^+-NEt_2, 17), 91 (M^+-SO_2NEt_2, 76), 84 (piperidyl cation, 100). (Found: M^+, 239.097. $C_{12}H_{17}NO_2S$ requires *M*, 239.098).

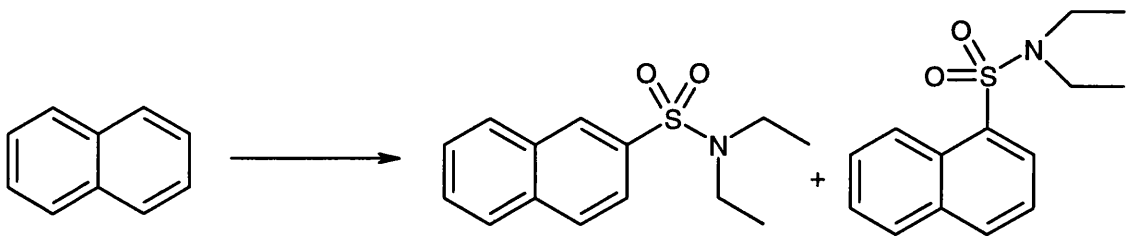
N,N-Dimethylnaphthalenesulfonamide 171[178]



171

Naphthalene (5 mmol) was sulfamoylated with *N,N*-dimethylsulfamoyl chloride (1 mmol) using the general procedure to provide 1- and 2-*N,N*-dimethylnaphthalenesulfonamide (34:66) as a colourless oil (isolated yield 99 %, 0.23 g). The data for *N,N*-dimethylnaphthalenesulfonamide was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 2.77 and 2.83 (s, 3H, α-**171** and β-**171**, Me), 7.49-8.78 (m, 7H, aromatic protons). δ_H (75.5 MHz, $CDCl_3$): β-**171**: 37.5, 124.5, 125.7, 127.2, 128.4, 129.2, 129.5, 130.8, 133.0, 134.7, 134.8. α-**171**: 38.1, 123.5, 127.9, 128.3, 129.2, 129.4, 129.6, 129.6, 132.6, 133.0, 135.2. *m/z* (EI^+) 235.0 (M^+, 100%).

N,N-Diethylnaphthalenesulfonamide 172[179]

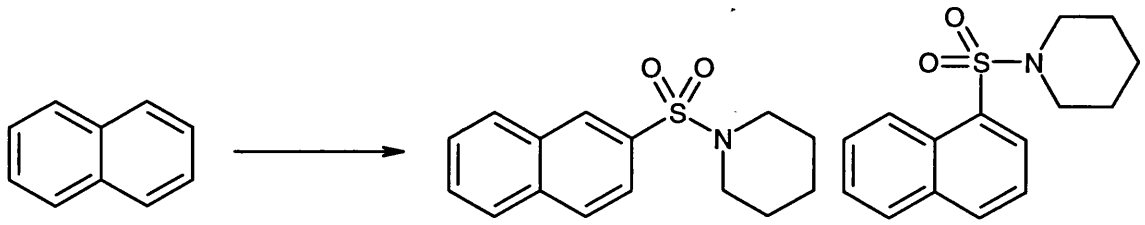


172

Naphthalene (5 mmol) was sulfamoylated with *N,N*-diethylsulfamoyl chloride (1 mmol) using the general procedure to provide 1- and 2-*N,N*-diethylnaphthalenesulfonamide (37:63) as a colourless powder (isolated yield 44 %,

0.12 g). The data for *N,N*-diethylnaphthalenesulfonamide was consistent with that found in the literature. mp 60-62 °C. δ_H (300 MHz, $CDCl_3$): 1.09 and 1.15 (t, 3H, β-**172** and α-**172**, *J* 7.2 and 7.1), 3.30 and 3.38 (q, 2H, α-**172** and β-**172**, *J* 7.1 and 7.2), 7.50 – 8.66 (m, 7H, aromatic). δ_C (75.5 MHz, $CDCl_3$): β-**172**: 14.2, 42.0, 122.5, 127.4, 127.9, 128.2, 128.5, 129.2, 129.3, 132.2, 134.6, 137.3. *m/z* (EI^+): 263 (M^+, 12 %), 248 (M^+-Me, 20), 191 (M^+-NEt_2, 25), 127 (M^+-SO_2NEt_2, 100). (Found: M^+, 263.098. $C_{14}H_{17}NO_2S$ requires *M*, 263.098).

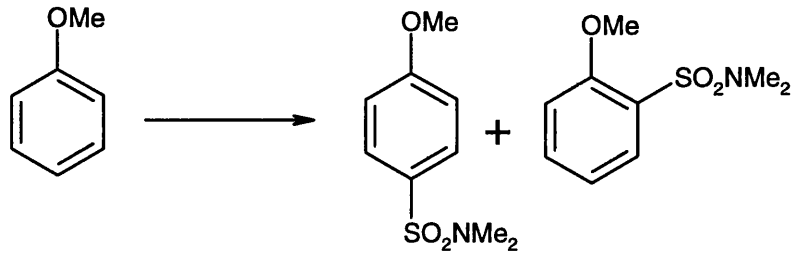
Piperidylnaphthalenesulfonamide 173[180]



173

Naphthalene (5 mmol) was sulfamoylated with 1-chlorosulfonylpiperidine (1 mmol) using the general procedure to provide 1- and 2-piperidylnaphthalenesulfonamide (24:76) as a colourless powder (isolated yield 44 %, 0.12 g). The data for piperidylnaphthalenesulfonamide was consistent with that found in the literature. mp 75-77 °C. δ_H (300 MHz, $CDCl_3$): 1.38-1.47 (m, 2H), 1.55-1.69 (m, 4H), 3.05 and 3.17 (t, *J* 5.5, 4H, α and β), 7.52-8.33 (m, ar. protons, 7H). δ_C (75.5 MHz, $CDCl_3$): β-**173** 23.6, 25.4, 46.4, 124.1, 125.3, 126.8, 127.9, 128.8, 129.0, 130.4, 133.2, 134.2, 134.3. α-**173**: 23.5, 25.2, 47.0, 123.1, 127.5, 127.8, 127.9, 128.7, 128.9, 129.1, 129.2, 132.2, 134.8. Elemental analysis (Found: C, 65.4; N, 5.0; H, 6.17. $C_{15}H_{17}NO_2S$ requires C, 65.4; N, 5.1; H, 6.22 %). *m/z* (EI^+): 275 (M^+, 24%), 127 (M^+-$SO_2N(CH_2)_5$, 69), 84 ($N(CH_2)_5$, 100). (Found: M^+, 275.098. $C_{15}H_{17}NO_2S$ requires *M*, 275.098).

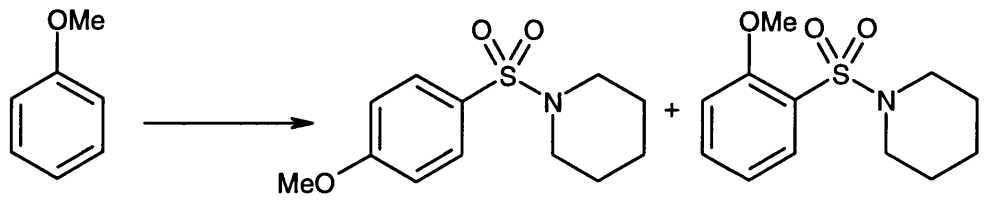
N,N-Dimethyl(methoxybenzene)sulfonamide 174[176]



174

Anisole (5 mmol) was sulfamoylated with *N,N*-dimethylsulfamoyl chloride (1 mmol) using the general procedure to provide 4- and 2-*N,N*-dimethyl(methoxybenzene)sulfonamide (55:45) as a colourless powder (isolated yield 99 %, 0.23 g). The data for *N,N*-dimethyl(methoxybenzene)sulfonamide was consistent with that found in the literature. mp 72-73 °C. δ_H (300 MHz, $CDCl_3$): 2.66 (s, 4-NMe_2, 6H), 2.84 (s, 2-NMe_2, 6H), 3.88 (s, 4-OMe, 3H), 3.92 (s, 2-OMe, 3H), 6.98-7.91 (m, aromatic, 4H). δ_C (75.5 MHz, $CDCl_3$): (4-**174**): 38.4, 56.0, 114.6, 127.4, 130.2, 163.3; (2-**174**): 37.7, 55.9, 112.2, 120.4, 126.1, 131.9, 134.4, 156.9. Elemental analysis (Found: C, 50.3; N, 6.3; H, 6.15. $C_9H_{13}NO_3S$: C, 50.2; N, 6.5; H, 6.10 %). *m/z* (EI): 215 (M^+, 3%), 171 (M^+-NMe_2, 14), 108 (M^+-SO_2NMe_2, 24), 44 (NMe_2^+, 100). (Found: M^+, 215.062. $C_9H_{13}NO_3S$ requires *M*, 215.062).

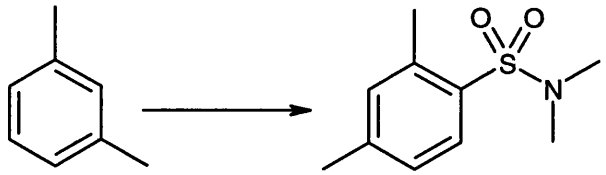
Piperidylanisylsulfonamide 175[181]



175

Anisole (5 mmol) was sulfamoylated with 1-chlorosulfonylpiperidine (1 mmol) using the general procedure to provide 4- and 2-piperidylanisylsulfonamide (64:36) as a colourless powder (isolated yield 80 %, 0.20 g). The data for piperidylanisylsulfonamide was consistent with that found in the literature. mp 85-86 °C. δ_H (300 MHz, $CDCl_3$): 1.36-1.45 and 1.45-1.56 (m, 2H, 4-**175** and 2-**175**), 1.56-1.69 (m, 4H), 2.96 and 3.20 (t, 4H, 4-**175** and 2-**175**, *J* 5.5), 6.97-7.91 (m, 4H, aromatic). δ_C (75.5 MHz, $CDCl_3$): (4-**175**): 23.5, 25.1, 47.0, 55.6, 114.1, 127.8, 129.8, 162.8. (2-**175**): 23.9, 25.8, 46.8, 55.9, 112.2, 120.3, 126.8, 131.7, 134.2, 156.9. Elemental analysis (Found: C, 56.3; N, 5.3; H, 6.68. $C_{12}H_{17}NO_3S$ requires C, 56.4; N, 5.5; H, 6.71 %). *m/z* (EI^+): 255 (M^+, 30%), 171 (M^+-$N(CH_2)_5$, 48), 156 (M^+-$N(CH_2)_5$-Me, 38), 84 ($^+N(CH_2)_5$, 100). (Found: M^+, 255.094. $C_{12}H_{17}NO_3S$ requires *M*, 255.098).

2, 4-*N,N*–Tetramethylbenzenesulfonamide 176[182]

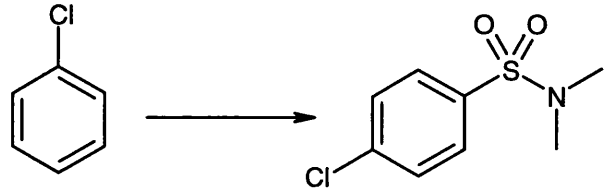


176

m-Xylene (5 mmol) was sulfamoylated with *N,N*-dimethylsulfamoyl chloride (1 mmol) using the general procedure to provide 2,4-*N,N*–tetramethylbenzenesulfonamide as a colourless oil (isolated yield 63 %, 0.13 g). The data for 2,4-*N,N*–tetramethylbenzenesulfonamide was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 2.37 (s, 3H), 2.59 (s, 3H), 2.78 (s, 6H, NMe_2),

7.10-7.13 (m, aromatic, 2H), 7.77 (dd, ^3J 8.7, 1H). δ_C (75.5 MHz, $CDCl_3$): 21.0, 21.7, 37.5, 126.8, 130.5, 132.9, 133.7, 138.1, and 143.5. Elemental analysis (Found: C, 56.3; N, 6.5; H, 7.10. $C_{10}H_{15}NO_2S$ requires C, 56.3; N, 6.6; H, 7.10 %). *m/z* (EI^+): 213 (M^+, 57%), 169 (M^+-NMe_2, 10), 105 (M^+-$SO_2NMe_2$100). (Found: 213.082, $C_{10}H_{15}NO_2S$ requires 213.082).

_N,N_-Dimethyl-4-chlorophenylsulfonamide 177[178]



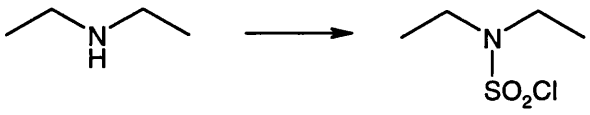
177

Chlorobenzene (20 mmol) was sulfamoylated with *N,N*-dimethylsulfamoyl chloride (1 mmol) using the general procedure to provide *N,N*-dimethyl-4-chlorophenylsulfonamide as colourless needles (isolated yield 99 %, 0.23 g). The data for *N,N*-dimethyl-4-chlorophenylsulfonamide was consistent with that found in the literature. mp 79-80 °C (lit.[178] 79-80 °C). δ_H (300 MHz, $CDCl_3$): 2.73 (s, 6H), 7.50 (d, *J* 8.7, 2H), 7.71 (d, *J* 8.7, 2H). δ_C (75.5 MHz, $CDCl_3$): 37.9, 129.1, 129.4, 134.1, 139.3. Elemental analysis (Found: C, 43.7; N, 6.2; H, 4.60. $C_8H_{10}ClNO_2S$ requires C, 43.7; N, 6.4; H, 4.60 %). *m/z* (EI):219 and 221 (M^+, 54% and 18%), 175 and 177 (M^+-NMe_2, 35 % and 13 %), 111 and 113 (M^+-SO_2NMe_2, 100% and 33 %), 75 (M^+-SO_2NMe_2-Cl, 33 %). (Found: 221.009. $C_8H_{10}ClNO_2S$ requires 221.009).

General Procedure for the Preparation of Sulfamoyl Chlorides

To a stirred solution of sulfuryl chloride (30 mmol) in dry chloroform (30 ml) at 0 °C under nitrogen was added a mixture of dialkylamine (30 mmol) and triethylamine (30 mmol) dropwise over 1 h. After stirring for an additional hour, the reaction mixture was diluted with water (20 ml) washed with 10% aqueous hydrochloric acid (20 ml) and dried ($MgSO_4$). The removal of the solvent gave an oil which crystallised partially. It was stirred with hexane (15 ml) and then filtered to remove solids. Concentration of the filtrate gave the crude product.

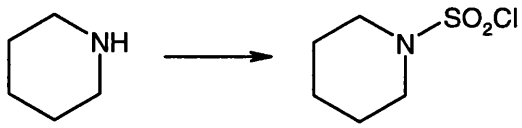
Diethylsulfamoyl chloride 167[84]



167

Diethylsulfamoyl chloride was prepared using the general procedure. Distillation of the crude product gave diethylsulfamoyl chloride (isolated yield 36 %, 1.75 g). The data for diethylsulfamoyl chloride was consistent with that found in the literature. bp 80 °C (6 mm Hg). δ_H (300 MHz, $CDCl_3$): 1.27-1.35 (t, 6H, *J* 7.2), 3.36-3.47 (q, 4H, *J* 7.2). δ_C (75.5 MHz, $CDCl_3$): 12.7, 45.0.

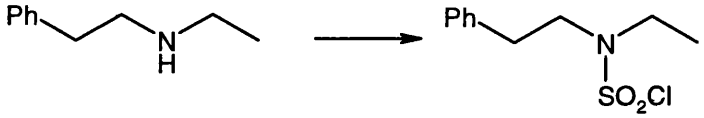
1-Chlorosulfonylpiperidine 168[84]



168

1-Chlorosulfonylpiperidine was prepared using the general procedure. Distillation of the crude product gave 1-chlorosulfonylpiperidine (isolated yield 40 %, 2.03 g). The data for 1-chlorosulfonylpiperidine was consistent with that found in the literature. bp 110 °C (5 mm Hg). δ_H (300 MHz, $CDCl_3$): 1.55-1.65 (m, 2H), 1.72-1.84 (m, 4H), 3.15-3.40 (m, 4H). δ_C (75.5 MHz, $CDCl_3$): 22.9, 24.4, 48.8.

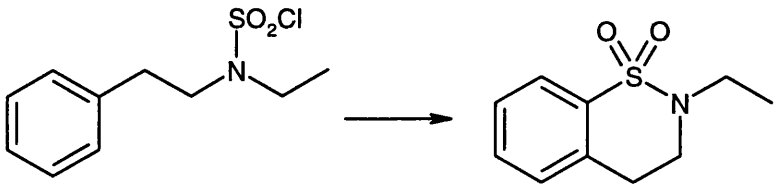
Ethyl(2-phenylethyl)sulfamoyl chloride 179



179

Ethyl(2-phenethyl)sulfamoyl chloride was prepared from (ethyl)phenethylamine (6.51 mmol) using the general procedure. Column chromatography (light petroleum : ethyl acetate, 4:1) of the crude product gave ethyl(2-phenethyl)sulfamoyl chloride which was used straight away (isolated yield 19 %, 0.30 g). δ_H (300 MHz, $CDCl_3$): 1.35 (t, 3H, *J* 7.2), 3.01 (t, 2H, *J* 7.9), 3.38 (q, 2H, *J* 7.2), 3.51 (t, 2H, *J* 7.9), 7.17-7.38 (m, 5H).

2-Ethyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide 180[183]

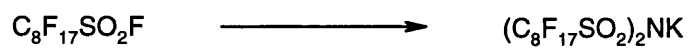


180

To a refluxing solution of indium triflate (0.24 mmol) in dry DCE (20 ml) with 4Å molecular sieves was added **179** (1.21 mmol). After stirring at reflux, the reaction was cooled and diluted with DCM (20 ml) and water (20 ml). The aqueous layer was back extracted with DCM (3 x 20 ml) and the combined organic layers were washed with saturated brine (25 ml), dried ($MgSO_4$) was concentrated *in vacuo* to afford the crude product. Purification by column chromatography (light petroleum: ethyl acetate, 4:1) gave 2-ethyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (57% isolated yield, 0.256 g). mp 59-60 °C (lit.[183] 60-61). δ_H (300 MHz, $CDCl_3$): 1.30 (t, 3H, *J* 7.2), 3.00 (t, 2H, *J* 6.4), 3.26 (q, 2H, *J* 7.2), 3.89 (t, 2H, *J* 6.4), 7.21 (ddd, ^3J 8.0, 1H), 7.36 (ddd, ^3J 8.0, ^3J 8.0, 1H), 7.43 (ddd, ^3J 8.0, ^3J 8.0, 1H), 7.81 (ddd, ^3J 8.0, 1H). δ_C (75.5 MHz, $CDCl_3$): 13.8, 23.7, 41.9, 44.4, 124.7, 127.5, 129.4, 131.9, 135.1, 137.0. Elemental analysis (Found: C, 56.5; N, 6.5; H, 6.15; $C_{10}H_{13}NO_2S$ requires C, 56.8; N, 6.6; H, 6.20 %). *m/z* (EI^+): 211 (M^+, 17%), 196 (M^+-Me, 100), 90 (M^+-$SO_2N(Et)CH_2CH_2$, 77). (Found: 211.067 $C_{10}H_{13}NO_2S$ requires 211.067).

6.7 Indium bis(perfluorooctanesulfonyl)amide

Potassium bis(perfluorooctanesulfonyl)amide 183[150]



183

To a 250 ml three-necked flask, fitted with condenser and thermometer, was introduced THF (40 ml), K_2CO_3 (29 mmol) and acetamide (11.2 mmol). The reaction mixture was warmed to 65 °C and perfluorooctanesulfonyl fluoride (11.2 mmol) was added dropwise over 30 min. After a further 3 h at 65 °C, additional perfluorooctanesulfonyl fluoride (11.2 mmol) was added dropwise over 30 min and the reaction was stirred at 65 °C for 24 h. On cooling, the reaction mixture was concentrated *in vacuo*, and the residue treated with acetone. Filtration removed KF and K_2CO_3, and the filtrate was concentrated. Addition of diethyl ether and filtration afforded crude potassium bis(perfluorooctanesulfonyl)amide. Recrystallisation with EtOH afforded potassium bis(perfluorooctanesulfonyl)amide as colourless needles (isolated yield 65%, 7.43 g). The data for potassium bis(perfluorooctanesulfonyl)amide was consistent with that found in the literature. δ_F (376 MHz, CD_3OD): -82.8 (t, 6F), -116.0 (t, 4F), -122.0 (m, 4F), -123.1 (m, 12F), -124.1 (m, 4F), -127.6 (m, 4F). Elemental analysis (Found: C, 17.2; N, 2.0; H, 0.05; $C_{16}F_{34}NO_4S_2K$ requires C, 18.8; N, 1.4; H, 0.00 %). ν_{max}(nujol)/cm^{-1} 1372 (S=O), 1300, 1157 (S-O).

Bis(perfluorooctanesulfonyl)imide 184

$$(C_8F_{17}SO_2)_2NK \longrightarrow (C_8F_{17}SO_2)_2NH$$

184

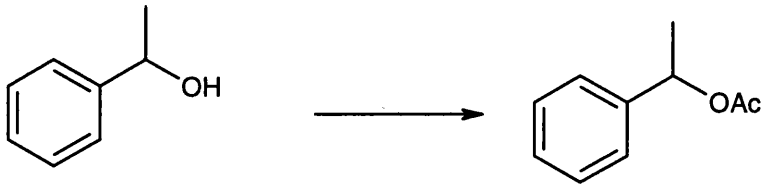
Potassium bis(perfluorooctanesulfonyl)amide (1.5 mmol) in a sublimation pot was treated with concentrated H_2SO_4 (15 mmol). Vacuum sublimation at 0.7 mm Hg and 100 °C afforded a colourless solid. The solid was dissolved in water (30 ml), treated with $BaCl_2$ (5 g) and extracted with diethyl ether (2 x 10 ml). Concentration of the organic layers afforded crude bis(perfluorooctanesulfonyl)imide as an amorphous solid. A second vacuum sublimation gave bis(perfluorooctanesulfonyl)imide as a colourless solid (isolated yield 96%, 2.77 g). δ_F (376 MHz, D_2O): –80.9 (m, 6F), -114.9 (m, 4F), -120.7 (m, 4F), -122.0 (m, 12F), -122.8 (m, 4F), –126.0 (m, 4F). ν_{max}(nujol)/cm^{-1} 3500 (N-H), 1663, 1366 (S=O), 1326, 1279, 1256 (C-F), 1203 (C-F), 1163 (S-O), 1079.

Indium(III) bis(perfluorooctanesulfonyl)amide 185

$$(C_8F_{17}SO_2)_2NH \longrightarrow [(C_8F_{17}SO_2)_2N]_3In$$ **185**

To a suspension of indium oxide (1 mmol) in water (10 ml) was added (Bis(perfluorooctanesulfonyl)imide (5.4 mmol) in water (5 ml). After stirring at reflux for 24 h, the reaction mixture was cooled, filtered, concentrated *in vacuo* and dried under high vacuum (0.5 mmHg) for 2 days to give Indium(III) bis(perfluorooctanesulfonyl)amide as an off-white powder (isolated yield 96%, 2.93 g). δ_F (376 MHz, CD_3OD): –82.8 (m, 6F), -115.9 (m, 4F), -121.9 (m, 4F), -122.9 (m, 12F), -124.0 (m, 4F), –127.5 (m, 4F).

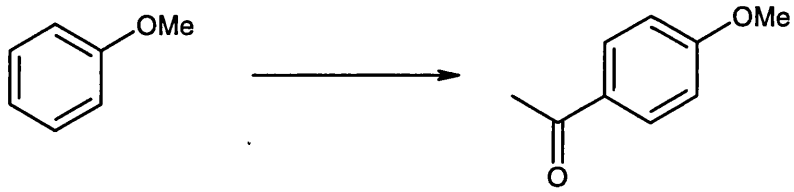
1-Acetoxy-1-phenylethane 187[184]



187

To a solution of *sec*-Phenethyl alcohol (7 mmol) and acetic anhydride (7 mmol) in toluene (2 ml) was added a suspension of **185** (0.07 mmol) in perfluoro(methylcyclohexane) (2 ml). The reaction mixture was stirred at 35 °C for 30 min and then cooled and partitioned. The organic layer was washed with water (3 x 5 ml), dried ($MgSO_4$) and concentrated to give 1-acetoxy-1-phenylethane as a clear oil (isolated yield 99%, 1.15 g). The fluorous layer was reused for further acylations. The data for 1-acetoxy-1-phenylethane was consistent with that found in the literature. δ_H (300 MHz, $CDCl_3$): 1.53 (d, 3H, *J* 6.6), 2.06 (s, 3H), 5.85 (q, 1H, *J* 6.6) 7.24-7.35 (m, 5H). δ_C (75.5 MHz, $CDCl_3$): 21.2, 22.1, 126.0, 127.8, 128.4.

Fluorous Phase Friedel-Crafts Acylation



97

To a solution of anisole (1 mmol) and acetic anhydride (1 mmol) in DCE (5 ml) in an Ace® pressure tube was added a suspension of **185** (0.1 mmol) in perfluoro(methylcyclohexane) (5 ml). The reaction mixture was stirred at 80 °C for 2 h and then cooled and partitioned. The organic layer was washed with water (3 x 5

ml), dried ($MgSO_4$) and concentrated to give 4-methoxyacetophenone as a clear oil (isolated yield 80%, 0.12 g). The data for 4-methoxyacetophenone was consistent with that obtained earlier (pp 115).

CHAPTER 7

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